AIDS TO ORGANOTHERAPY

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# ORGANOTHERAPY

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# PREFACE

THIS small book aims at summarising our knowledge of organotherapy To enable the reader to grasp the basis of this method, the physiological facts which are relevant to the various secretions have been dealt with at some length, and those secretions which stand most firmly upon physiological and clinical evidence have received the most consideration

From the therapeutic aspect, the thyroid is pre-eminent, and it has been considered that a relatively large part of the book might with advantage be devoted to this gland and its extract, for here the reader unfamiliar with organotherapy will find a satisfactory extract with which to become familiar, first in theory and then in practice

Small space has been devoted to the less well-recognised extracts as it has been felt that those sufficiently interested to follow up this subject into the realms of speculation can consult larger works for additional data

As few references as possible have been given, in order that the reading of the book may be simplified The bibliography contains a list of books to many of which the author is indebted for much material quoted in the text

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# AIDS TO ORGANOTHERAPY

## CHAPTER I

### INTRODUCTION

ORGANOTHERAPY is a method of treating disease by means of preparations manufactured from the organs of animals The name is of recent origin, but the ideas underlying this method are of great antiquity. The ancients were in the habit of prescribing weird combinations of animal organs for the cure of various disorders, but such treatment was intimately mixed up with witchcraft, exorcism, and incantation Nevertheless, it may be said to have been the precursor of the principles of organotherapy as we understand it to-day, with this difference, that the exhibition of organic extracts in modern times is founded upon more accurate pathology, and while it is still empirical in many of its branches, it is no more so than much of the prescribing of inorganic drugs

While the ancients relied upon such remedies as "eye of newt and toe of frog," the physician of to-day collects his symptoms into a syndrome, by the study of the actions of the various organs in a particular case, and utilises a preparation of an organ or organs which has been manufactured with careful atten-

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tion to detail So that the success of treatment by this method depends upon the correlation of the physiologist, who traces the symptoms produced by experimental interference with the physiological harmony, the physician, who discovers analogous symptoms in the patient, and the practical chemist, whose work concerns the handling of the animal organ, the extraction of its chemical constituents, and its conversion into a form suitable for administration to a patient

Organotherapy is founded upon the discoveries of the endocrine glands and the part they play in maintaining health It has been shown that in normal health there is an " endocrine balance "—that is to say, the various ductless glands supply chemicals which are needed by the body, but these are maintained at what we may call a " physiological level " " All glands, whether they have excretory ducts or not, give to the blood useful principles, the absence of which is felt when they are extirpated or destroyed by disease " The comparison of a gland possessing a duct with a " ductless gland " will help us to understand the position as regards organotherapy The former produces a secretion which is poured down the duct and utilised for the purpose for which it is separated from the body of the gland; examples of this are the salivary and gastric glands, the pancreas and the seminal vesicles The ductless glands on the other hand have no structure such as a duct whose sole use is the distribution of the product of the gland The secretion manufactured by their activity has to find its way direct into the blood-stream the most important examples of such glands are the thyroid and suprarenals The term " secretion " is confined to the production by a gland of a

chemical substance which is utilised in the body; while the use of the term "excretion" is confined to a substance cast off from the body

But the internal secretions are not produced solely by the ductless glands Many glandular structures possess both an internal and external secretion, examples of which are found in practically all the important organs of the body The liver, pancreas, testicles, and ovary—to mention only a few—have been shown to influence metabolism by means of their internal secretion, and physiologists have shown that the retention of the internal secretions of these glands is vital to the maintenance of the bodily health

The practice of organotherapy has arisen from an attempt to replace a secretion or secretions, presumed to be missing, by the administration of an analogous product obtained from an animal The history of this form of treatment may be said to have arisen from the work of Brown-Séquard, although from the practical standpoint by far more important results have accrued from subsequent work in relation to the thyroid gland

Brown-Sequard experimented with subcutaneous extracts of the testicle, and found that they exercised a most beneficial result upon himself The reasoning behind this is sound, inasmuch as this is one of the secretions which is deficient in old age, and therefore this observer considered that senility might be the drying-up of the secretions of these glands He reported a marked rejuvenating effect after this treatment, but subsequent work has not carried out this early promise to the extent which Brown-Sequard's work had led us to hope

Quite a different result can be recorded from the

administration of thyroid extract. In fact, it is not an exaggeration to refer to this branch of organotherapy as having produced brilliant results—results which have revolutionised the treatment of certain disorders Cretinism and its elder brother myxœdema stand at the head of this list, but there follows a multitude of other ailments, some trivial, some more serious, in which extract of the thyroid gland can be given with confidence that the health and well-being of the individual will be improved by its administration

We shall discuss the principles of organotherapy in detail in a subsequent chapter Suffice it to say here that this "substitutive" therapy is only one of the ways in which organic extracts are utilised, it has been referred to at this place because it ushered in a method of treatment which has since received a wide amplification in other directions One of these runs upon lines parallel with the exhibition of inorganic chemicals—namely, the "specific" employment of an organic product because its properties produce certain results which are desired in a given case The use of pituitary and suprarenal extracts at once occurs to us as an example of this use The former has been adopted in gynæcological practice for its use on the uterus the surgeon utilises it for cases of "shock," while the physician prescribes it for many conditions which we shall enumerate in a subsequent chapter

The use of pituitary in gynæcological practice is an example of the application of an organic product for its physiological action Others will readily occur to the reader the usefulness of adrenal extract for its specific action on the vaso motor system is an analogous example

From beginnings such as those of Brown-Séquard,

and those who followed his example, has arisen a method of treatment which, in one way or another, affords an additional therapeutic agent often of the greatest service The physiological observations of Claude Bernard, the researches of Schiff, the later work of Vassall and Gley, of Biedl, and many other physiologists, have brought to light the importance of the internal secretions, and the intimate correlation existing between the various humours of the body.

Gull and Ord had observed in 1872 the symptoms of myxœdema, while a few years later Schiff published his work "On the Effects of the Removal of the Thyroid Body" In 1883 Kocher recorded his observations upon myxœdematous conditions ensuing after the removal of the thyroid gland G R Murray in 1891 published the results of administering the thyroid gland, and these were so striking, that it may be said, without hope of contradiction, that the field of utility of thyroid extract has been widening ever since Nowadays thyroid extract is in use for the treatment of a large variety of disorders, indeed, its utility has become so well known, that it figures in the daily press from time to time as a rejuvenator of old age!

Turning for a moment to the therapeutic aspect of other of the internal secretions, we find that their properties from the clinical point of view are not so well defined, and the results claimed from their administration are not so striking It may be that from Brown Séquard's original observations too much was expected from subsequent researches, clinicians hoping for specific results by administering gland extracts of an organ found to be diseased That this claim cannot be substantiated has been shown in Addison's disease, where no substantial impr-

ment has been obtained by the administration of extract of the suprarenal gland, except perhaps in chronic cases

But this is not true for all disorders arising from interference, by growth or otherwise, with the functioning of a gland As we shall see in a later chapter, extract of pituitary, of the ovary, testis, mammary gland, and liver, of the intestinal glands, spleen, and so on, can be prescribed in certain deficiency diseases with very real benefit Again, pluriglandular preparations are useful, one of the best of these, manufactured from the nervous system, being widely used with excellent results in certain of the neuroses

In organotherapy the work of the clinician is of the first importance He has to rely upon the physiologist for the data upon which he founds his treatment, but the utility or otherwise of organic products rests for proof on his hands, for he, and he alone, is working with the living human being This is shown by pluriglandular preparations, for there is no laboratory support for the administration of nervous tissue in organic disease of that tissue, yet there is widespread clinical testimony to the efficacy of preparations of this nature The present writer has seen marked improvement in such diseases as paralysis agitans from this treatment, but has yet to learn in what manner this beneficial result is achieved

Again, in functional derangements, which form the bulk of the cases the medical man is called upon to treat, organotherapy, judiciously applied, will often work wonders and will turn the scale between well-being and ill-health The truth is that all workers in this field are convinced of the future which lies in

front of organotherapy, while admitting that, in its present stage of development, results achieved in practice often remain unexplained in theory. Nevertheless, laboratory work is but the beginning of medicine, and points the way to the physician; the latter must build up his therapy from facts collected at the bedside He alone can collect clinical facts which are of value, and the comparison of his results with those achieved by experimental physiology must, in time, solve many problems which are at present unexplained

## CHAPTER II

# THE PHYSIOLOGY OF THE INTERNAL SECRETIONS

### Introductory.

In the former chapter we discussed briefly the history of organotherapy, and some of the earlier work upon which the practice of to-day is founded. In this chapter we propose to describe in more detail the physiological principles which govern organotherapy.

It is recognised that the various organs of the body, the work of which constitutes life, are interdependent, and not as was formerly thought, individual systems. Further, it is now known that many of the messages which pass from one organ to another are chemical in nature and not nervous. Morphologically, the nervous system is comparatively late in development, but the responses of the most primitive forms of life are chemical. This is well shown in the work of the gastro intestinal tract, where the saliva stimulates the gastric secretion, the gastric the pancreatic, and so on. That the first messages in digestion are nervous is well recognised, for the saliva is secreted before the food enters the mouth, the gastric secretion is likewise so stimulated, as Pavlov showed, but the work is carried on by chemical messengers.

For these chemical messengers, whose presence in

the blood-stream stimulates the activity of the organs, Starling suggested the name of "hormone" (ὁρμάω, "I excite"). As these chemical messengers play an important part in the theory which underlies organotherapy, we must describe their physiology in some detail

### Hormones.

Schäfer says: "Material which is passed into the blood or lymph from any tissue or organ of the body forms its internal secretion, and organs which are not known to possess any other function than that of passing such material into the blood or lymph are internally secreting or endocrine organs"*

As is well known, not only glands without ducts (the "ductless glands"), but also glands with ducts, possess an internal secretion which produces results of prime importance to the bodily harmony In the digestive tract the pancreas has been shown to secrete a chemical substance whose presence in the blood-stream enables sugar to be stored in the liver Removal of the pancreas was shown by von Mering and Minkowski to produce glycosuria for the absence of its internal secretion prevented the sugar-storage function of the liver It has been assumed that special cells, the "islets of Langerhans," are responsible for the production of this internal secretion, for they are found in masses of irregular shape, their connection with the ducts is not evident, and more striking still, they have been found to be atrophied in some cases of diabetes These cells may be regarded, therefore as an organ of internal secretion

Again, it has been shown that the duodenal epithelium possesses an internal secretion the function

* "The Endocrine Glands," p 1

of which is to stimulate the pancreas to pour out its digestive juice Formerly the secretion of the pancreas was supposed to be due to "reflex action," but Bayliss and Starling in 1902 showed that it was caused by a chemical agent. These observers called the inactive chemical contained within the cells of the duodenum "pro-secretin", while the actual hormone produced by the action of the gastric juice upon the pro-secretin they named "secretin."

The name "hormone" has been given to these internally secreted chemical substances, but Schäfer has suggested that the name should be confined to such substances as excite another secretion. Some internally secreted substances inhibit the function of another secretion, an example of this is to be found in the placenta, an extract of which, when injected, tends to prevent the secretion of milk To these substances Schafer has applied the name "chalone," while he proposes to apply the term "hormone" only to those chemical agents which excite another secretion into activity. His term for the internal secretions is "autacoid," which includes both hormones and chalones

The word "hormone," however, has come into general use to indicate the "chemical messengers," and its use in this volume will be in this sense

## The Endocrine Glands.

The principal glands belonging to this group are the thyroid, suprarenal, and pituitary Each of these glands secretes a chemical messenger, which has a definite action in regulating the bodily metabolism, and their interaction is an important factor in maintaining what has been called "the endocrine balance"

Their effects have been proved by three methods—namely, oral administration, subcutaneous or intramuscular injection, and intravenous injection

Administration by mouth, notably in the case of the thyroid, of an extract of one of the glands belonging to the endocrine group, has marked effects, more particularly in individuals suffering from thyroid insufficiency, or endemic goitre, myxœdema, submyxœdema, and cretinism. Subcutaneous or intramuscular injection of an endocrine extract produces, in many instances, changes which are more speedily exhibited than when the same extract is administered orally; but the immediate effects of an intravenous injection are infinitely more striking The introduction of thyroid extract into a vein is followed by a fall of blood-pressure, suprarenal extract thus administered produces contraction of bloodvessels, flow of saliva, erection of hairs, dilatation of the pupil, while pituitary extract contracts the blood-vessels, causes increase of the renal secretion and of the mammary gland, contraction of the uterus, intestines, and plain muscle of the genitals (Schäfer)

Oral administration of the bodily hormones is in wide and general use, indeed, it may be said that this is the most usual method of exhibiting these substances But more recently the hypodermic or intramuscular route has been utilised with considerable success, although this method has been employed for some years in cases where the effect of the hormone was urgently required—*e g*, the use of pituitary extract in shock, uterine inertia, etc Sterile extracts of the various hormones, in a medium of olive oil or saline, and contained in ampoules, are put up by manufacturing chemists, and polyglandular extracts can likewise be utilised in this form Langdon

Brown divides the endocrine glands into two groups: (1) The adrenals with other chromaffin tissues, the pituitary, thyroid, and interstitial cells of the reproductive glands, (2) the mucosa of certain parts of the alimentary tract, the pancreas, and the parathyroids The first group, he states, interact chiefly with the sympathetic and are accelerators, the latter with the parasympathetic and are retarders.

## The Sympathetic System.

It may be useful at this place to give a brief account of the relations of the sympathetic system with the endocrine glands The sympathetic is now recognised to consist of two parts—the autonomic and the sympathetic proper The former is found in close relation to the third, seventh, and ninth cranial nerves, and the first three sacral nerves It does not supply centrifugal rami communicantes to the ganglia which lie on the bodies of the vertebral column The sympathetic portion forms chains of ganglia that receive the rami communicantes from the spinal cord, and it also includes the visceral ganglia (R H Rows) These two divisions are antagonistic to each other in regard to the separate functions of the organs

The secretions of the endocrine glands have a selective action on the two parts of the vegetative nervous system just described Adrenalin for example, stimulates the entire sympathetic system; pituitary the autonomic Again some of these secretions stimulate glands in the endocrine circle, others inhibit while the balance is maintained by the interaction of all the internal secretions There is an interaction between the chromaffin tissue on the

one hand, and the thyroid and pituitary on the other; while all three—chromaffin tissue, thyroid, and pituitary—exert an inhibitory action on the pancreas Another example of an inhibitory action is that of the interstitial gland of the testicle, and the secretion of the thyroid and the pituitary. The tone, therefore, of the visceral nervous system appears to be controlled by the secretions of the various glands of the endocrine group

## A Classification of the Endocrine Glands.

Noel Paton says "Every tissue probably yields products which may act upon other tissues, but the name 'endocrine glands' may conveniently be reserved for those structures which yield a product having some definite and specific action, not necessarily of the nature of excitation" He classifies the endocrinous glands *according to their seat of origin, as follows*

1 From the nervous system—
    Chromaffin tissue
    Hypophysis cerebri
2 From the buccal cavity—
    Thyroid
    Pituitary
3 From the intestine—
    Pancreas
    Mucosa of small intestine
4 From the branchial arches—
    Parathyroids
    Thymus
5 From the mesothelium of the genital ridge—
    Gonads
    Interrenal bodies *

* "Regulators of Metabolism," pp 35, 36

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* "Regulators of Metabolism," pp 35, 36

## The Thyroid and Parathyroids.

The thyroid stands predominant amongst the endocrine glands, for its activities are widespread, and there are relatively few metabolic processes in which the secretion of this gland is not concerned

It has a close association with the sympathetic system, the chromaffin tissue, and the gonads Its over-action in Graves' disease, where it responds to sympathetic irritation, is well known; it tends to enlarge at those periods of life where genital changes are conspicuous, examples of which are puberty, marriage, and pregnancy. The interrelation between the thyroid gland and the secretions of the genital organs is thus plain. Again, the thyroid gland is one of the organs through which the mind expresses itself, and it tends to react to distressing emotions by over-secretion Many examples of this were seen among soldiers suffering from shell-shock and other war neuroses, and among civilians after air-raids

The thyroid proper, as distinct from the parathyroids, is an organ consisting of small closed vesicles, mostly irregularly spheroidal in shape Each vesicle is lined by epithelium, which varies between columnar, cubical, or flattened The blood-supply of the gland is very free, the thyroid being one of the most vascular organs of the body The nerve-supply is derived from the sympathetic and the superior and inferior laryngeal nerves

The vesicles contain the " colloid " material which is characteristic of the gland. This substance is insoluble in alcohol, water, and ether; when coagulated it is stained by eosin and hæmatoxylin (Schäfer) It is believed to form a storehouse for the secretion which is typical of the gland

The thyroid gland develops as a median growth from the floor of the pharynx between the first and second branchial pouches. It appears early and grows backwards, bifurcating into two lateral columns. The thyroglossal duct is formed from a solid column of cells, but becomes obliterated, leaving the foramen cæcum at the back of the tongue as a permanent relic of its existence. This duct possesses a peculiar interest for the student of [illegible]

[illegible]

[illegible] for the ease with which thyroid extract is absorbed by ingestion.

The parathyroids are four in number, and are arranged in pairs, two lying on each side of the mid-line in intimate relation to the thyroid gland. Both pairs are supplied with blood by branches of the inferior thyroid artery. The upper thyroid-parathyroid is often found deeply embedded in the substance of the thyroid gland, and has been called the "internal" parathyroid, the lower receiving the name of "external" parathyroid. Schäfer, however, prefers to call them parathyroid III and parathyroid IV. They are minute organs, composed of epithelium-like cells, arranged in one of two ways. They are either formed into a compact mass, or divided into lobules by strands of connective tissue. There is a capsule around the gland. Two types of cells occur in the gland—the ordinary, small, clear or granular, and larger cells containing oxyphil cells, fatty granules and sometimes glycogen. Cells are also found resembling those characteristic of the thyroid. The colloid is believed to differ from that present in the thyroid, by reason of its containing no iodine. The blood-supply is extremely free. The

parathyroids are developed from the third and fourth visceral pouches, which also give rise to the thymus gland. The sympathetic stimulates the thyroid, and the thyroid secretion "lowers the threshold to sympathetic stimulation." After a varying time the thyroid tends to become exhausted, and we see patients who have symptoms pointing to a combination of hyperthyroidism and myxœdema. Normally the thyroid can store up its secretion, but when it becomes drained of its iodothyrin, it produces a clinical picture which is a combination of sympathetic over-stimulation and thyroid deficiency.

Deficiency in the secretion of this gland leads to well-marked bodily changes, which have received the name of myxœdema. We need not describe them here, as they find full recognition in all text-books of medicine. Lesser degrees have also been carefully described by Hertoghe.* Reference will be found in a subsequent chapter to the therapeutic use of thyroid extract to counteract these abnormalities.

The active principle of the thyroid secretion has been named "iodothyrin," and is a substance rich in iodine and nitrogen. The amount of this hormone varies according to the state of the bodily health, and it must be regarded as having a specific action on the nervous system. When administered by the mouth, thyroid extract is rapidly absorbed and causes loss of weight, mainly by increased diuresis, partly by increase in the nitrogenous waste. In large doses it causes a rise in the bodily temperature and pulse-rate, and it may produce glycosuria. These points should always be borne in mind when administering this substance to patients.

* I have given a full description of these in "The Organs of Internal Secretion," chapter iv, p. 91.

It has been said (Gilbert and Herscher) that thyroid extract diminishes the amount of bile-salts in the urine, and Langdon Brown confirms this, and states that he has relieved the pruritus of jaundice in several cases by the administration of thyroid extract. This extract has also been used in disorders ranging from obesity to ununited fractures.

## The Pituitary.

This gland consists of three parts—the pars anterior, the pars intermedia, and the pars posterior. It has a double origin, partly from nervous and partly from epithelial tissue.

### (a) *The Anterior or Glandular Part.*

This is the largest part of the gland, and is composed of glandular elements. It secretes a colloid, not unlike that of the thyroid, which appears to exert an action upon the bodily temperature, growth, cutaneous tissue, and sexual organs. The removal of the gland produces a fall in temperature, and the fact that an injection of pituitary extract causes a rise in temperature has been utilised for purposes of diagnosis of pituitary deficiency. Experimental removal of the lobe in young animals causes retrogressive changes in the sexual organs, with delay in the appearance of the secondary sexual characteristics. Hypo-pituitarism is associated with increase in the sub-cutaneous fat, a low body temperature, a smooth skin, amenorrhœa in the female and impotence in the male. Cushing, whose experiments on the pituitary have thrown much light upon its functions, concludes that it is the removal of the anterior lobe which gives rise to symptoms, but the extirpation of the posterior

lobe gives rise to no symptoms After experimental removal of the pituitary in animals, symptoms arise in thirty-six hours to two weeks These consist of uncertain movements of the muscles, bodily inactivity, subnormal temperature, and finally coma and death This condition has been called "cachexia hypophyseo-priva" Changes were found in the thyroid and the testis The same observer is of the opinion that acromegaly and gigantism are due to over-secretion of the anterior lobe of the pituitary.

(b) *The Pars Intermedia.*

The influence of the pars intermedia makes itself felt mainly in regard to metabolism This part of the gland is distinguished from the anterior part by the character of the cells, these appear as a well-marked layer, which also extends as a thin layer over the posterior part or pars nervosa The two portions of the cells of the pars intermedia are frequently found extending into the pars nervosa. It has been pointed out by Herring that the hyaline and granular globules derived from the cells of the pars intermedia pass into the pars nervosa, and can be traced as far as the continuation of the third ventricle into the stalk (Schafer), he therefore concludes that these substances form the secretion of this part of the pituitary, and that this secretion passes into the cerebro-spinal fluid

In over-activity of the pars intermedia (such as occurs in acromegaly), hyperglycæmia is found, and lowered sugar tolerance As Cushing has pointed out, in the later stages of this disease, a condition of hypopituitarism is frequent with the opposite metabolic condition—*i e* hypoglycæmia and raising of the sugar tolerance. This transference from over-action

to under-action has been termed "dyspituitarism" and is analogous to the condition which occurs in the thyroid gland in some instances of Graves' disease

(c) *The Posterior Lobe, or Pars Nervosa*

The posterior lobe of the pituitary gland, or infundibular body, is formed almost entirely of neuroglial fibres with some neuroglial cells scattered amongst them There are also ependyma cells to be found in the pars nervosa Between the neuroglia fibres, hyaline and granular matter is found, collected together into groups which are sometimes traceable to the infundibulum or stalk of the gland The physiological effect produced by extracts of this part of the gland is due to this material, for ordinary neuroglial extracts have no such action

This is the least vascular portion of the pituitary gland, and its blood-supply is not nearly so free as either the anterior portion or the pars intermedia

## The Suprarenal Glands

These small bodies, situated behind the peritoneum, and in front of the upper part of each kidney, constitute an important member of the group of ductless glands Their importance was first recognised when Addison, in 1855, described the disease which still bears his name, and attributed the symptoms to degeneration of these bodies

Addison's disease, as is well known, is characterised by general debility, great and increasing exhaustion, feeble cardiac action, low blood-pressure, and disturbances of the gastro-intestinal tract. As the disorder advances, [illegible] mptoms increase, and anæmia and [illegible] added [illegible]

picture The sign which is perhaps the most striking in the disease is the bronzing of the skin The cause of this is not known, but it has been suggested that it may be due to the fact that adrenalin is derived from the same source as the melanin of the skin, and that interference with the formation of adrenalin results in an excessive production of melanin

The adrenal glands consist of two parts—a cortex and a medulla The former consists of polygonal cells arranged in two columns—the outer (zona fasciculata) ending near the surface of the gland in rounded terminations (zona glomerulosa); the inner (zona reticularis) consisting of a network of trabeculæ, and lying adjacent to the medulla Lipoid granules are found in the cells of the cortex, which is yellowish in colour in consequence of their presence The cortex is rich in lipoids and fats, an analysis by Biedl showed that the suprarenal of the pig contains 38 88 per cent of lipoids in total solids of the organ, and as *Schäfer says, the medulla being poor in lipoids,* the proportion of these substances in the cortex must be very high Besides the lipoids, a doubly refracting substance is found in the cortex, and Elliott and Tuckett regard both the fatty and these latter substances as products of secretion of the cells (Schäfer)

The medulla of the gland is a highly vascular structure composed of cells permeated by sinus-like bloodvessels These cells are irregularly polygonal in shape, but "where they abut on the sinuses they often assume a more columnar aspect There can be little doubt that the materials they secrete find their way directly into the blood within the blood spaces"*

The whole gland is enclosed in a loose capsule surrounding the cortex, which appears as a brownish-

* "The Endocrine Organs," p. 54

yellow mass, while on section the medulla is seen to be brownish-black in appearance The two parts of the organ are morphologically distinct, the cortex being formed from mesoblastic tissue, derived from the genital ridge, the medulla belonging to the same group of epiblastic masses which gives rise to the sympathetic ganglia The cells of the medulla stain darkly with chromic acid, due to the presence of its characteristic chemical—adrenalin

The chromaphil substance isolated from the medulla of the suprarenal gland has been given the name *adrenalin* (Takamine) It has been isolated by this latter observer in a crystalline form, its formula being ortho-dioxyphenyl ethanol-methylamine *tyrosine* being oxyphenyl-amino-propionic acid In 1894 Oliver and Schäfer published the results of injecting extract of the suprarenal gland, and described the immediate rise of blood-pressure which followed—caused by contraction of the peripheral arteries—the slowing of the heart s action, and the diminution in the depth of the respirations As the change in the vessels occurs after severance of all the nerves to the vessels and even after complete destruction of the central nervous system, the effects must be due to direct chemical action But in the case of suprarenal extract these changes only occur in tissues supplied by the sympathetic nervous system other actions of the extract are upon involuntary nervous tissue supplied by the sympathetic fibres (sphincters of pylorus and of ileo-cæcal valve, spleen, vagina, etc ) It also exerts an action on the plain muscles of the orbit, so that the eye tends to protrude and the palpebral fissure to enlarge *

* For further details of great interest in this connection see 'The Endocrine Organs," pp 58–67

Langley points out that the result of suprarenal injection is identical with that of stimulating the endings of the sympathetic nerves Oliver and Schäfer showed that the *contractions of skeletal muscle are* prolonged under the influence of suprarenal extract; but they have since failed to get any effect with small doses of that substance.

The results of intravenous injection are very quick, while subcutaneous injections do not produce the characteristically rapid result Subcutaneous injection of adrenalin has been found to produce hyperglycæmia and glycosuria, this would appear to be due partly to its action upon the pancreas, partly to an action upon the liver nerve-endings.

*Extracts of the adrenals can be administered by* the mouth in large doses without producing any immediate physiological result.

### The Generative Glands of the Male.

The connective tissue situated between the tubules of the testicle is characterised by epithelium-like cells. This character was first discovered by Leydig in 1850, and the cells have been named after him—the cells of Leydig, or the *interstitial gland.* They vary in extent in different animals, *and appear to be better* developed in animals which rut when the seminiferous tubules are inactive If the circulation and nerve-supply of the testicle is interfered with, as by ligature of the whole of the spermatic cord, the interstitial cells share in the general atrophy.

[illegible] change, com-
po[illegible] les, and
ox[illegible] *cells of*
Leydig are functioning (even where the gland itself

is abnormal, such as in cryptorchids, and where the vas deferens has been ligatured), the secondary sexual characters develop and sexual desire is normal "Loewy found male secondary characters developed in caponised cockerels fed with testicle-substance." It would appear, therefore, that the development of male secondary characteristics is dependent upon a hormone secreted by the testis, and this is probably produced by the interstitial gland This is borne out by a number of observations, some of which are of great interest in this connection, tumours of the testicle have been found in children associated with the premature appearance of the secondary sexual characteristics, which have disappeared upon the removal of the tumour

If castration is performed after puberty, the secondary sexual changes may retrogress, and the accessory gonads—*e g*, the prostate—may show atrophic changes, but so long as there is no interference with the cells of Leydig, these changes do not occur After castration, the chief changes are those of metabolism, with the increased tendency to fat formation while glycosuria is curiously enough, more easily produced It seems undoubted that there is enlargement of the pituitary after castration, and this fact may account for the increase in length of the bones seen in the human subject (eunuchism) The adrenals are also increased markedly in size after castration, whereas after removal of the ovaries this is not so, the adrenals being small in the latter case (Hatai)

* Schafer *loc cit* p 135

## The Generative Glands in the Female.

The ovary contains a vascular stroma of connective tissue characterised by numerous spindle-shaped cells. There are also to be found in this stroma groups of cells differing in appearance from the spindle-shaped cells, and these have been termed "interstitial cells," and have been considered to be analogous to the cells forming the organ of Leydig. They differ, however, in two important characteristics—they are not so definite, and they are destroyed by X rays. They cannot, therefore, be stated to be an organ strictly analogous to that found in the testis.

The effects of removing the ovaries are as follows: Characters similar to those seen in the male develop, the mammæ remain undeveloped, there is absence of menstruation, and the hirsutes do not take on the appearance typical of the sex. If the operation is performed after puberty, these changes are not all seen, but there is amenorrhœa, and atrophy of t' mammæ sometimes occurs, there is diminution the size of the uterus and Fallopian tubes (in animals-Carmichael, Marshall, Jolly), the suprarenal gland are diminished, and the pituitary is only slightly enlarged compared to the marked hypertrophy seen after removal of the testis. The general body-weight tends to increase, with the formation of adiposity. As is the case after castration, most of the ductless glands are affected in some way, the size of the thyroid being lessened that of the pituitary increased, but less so than in the male, while the thymus does not show the retrogressive changes characteristic of this gland.

The physiological effects of injecting extract of the ovary (interstitial cells) is recorded by Schafer in

"The Endocrine Glands" It would appear from the results recorded that ovarian extracts contain two substances, one being an excitant, while the other is a depressor, so far as its action upon the uterus is concerned Injections of the extract of the interstitial cells produced inhibition of the normal rhythmic movements, and lowering of the tone of the uterine muscle, whereas extract of corpus luteum, when injected, caused a secretion of milk, which result was not obtained in extracts of ovary not containing corpus luteum It has been shown that the corpora lutea are related to the development of the mammary gland during pregnancy, experiments have shown that if they are destroyed during pregnancy the mammary gland fails to develop

The internal secretion of the ovary is also concerned with the formation of the uterine decidua and the fixation of the embryo

The uterus has been stated by some observers to furnish an internal secretion, which is believed to stimulate the formation of the corpus luteum Against this is the result of experiments which appear to show that typical development of the ovaries has been obtained in animals from whom the uterus has been removed

The mammary gland is believed to secrete a hormone which exerts a galactagogic effect, one observer states that injection of this extract has resulted in an increased flow of milk, while it has been known to produce abortion in pregnant animals

It has been suggested that the placenta furnishes a hormone whose function is to stimulate the function and growth of the mammary gland, while inhibiting the flow of milk There are objections to the acceptance of this theory which we need not enter into here

## The Pancreas and Duodenum.

In 1869 Langerhans discovered small isolated masses scattered throughout the pancreas, which have been named after him, "the islets of Langerhans." These small groups consist of polygonal cells, more freely supplied with capillary vessels than the rest of the gland, and quite distinct from the alveoli in character They have no communication with the ducts or alveoli The number of the alveoli is very variable

In 1902 Bayliss and Starling discovered that the injection of an extract of the duodenal mucous membrane produced a rapid secretion of pancreatic juice The extracts utilised had been treated with acid, without this the observers obtained little or no action They concluded that the hormone present in the duodenal mucous membrane (pro-secretin) becomes activated by the presence of acid and converted into secretin Evans discovered that pro-secretin disappears from the duodenal mucous membrane after removal of the pancreas This observation appears to show that the two hormones—that of the islets of Langerhans and of the duodenal lining—are mutually interacting An analogous hormone was isolated by Edkins from the pyloric mucous membrane This substance stimulates the gastric secretion, and has been termed gastrine

It was shown by von Mering and Minkowski that extirpation of the pancreas was immediately followed by hyperglycæmia and fatal diabetes No such effect followed ligation of the pancreatic duct, even when the gland becomes atrophic It was therefore concluded that the islets furnished an internal secretion, whose function is to regulate carbohydrate metabolism In support of this, experiments have shown

that diabetes does not occur if a graft of the pancreatic tissue is made into the body, but that it does occur if the graft be removed. Again, it has been found on many occasions that atrophy of the islets is present in cases of diabetes in man

The above facts make it evident that there is a secretion of the pancreas, which regulates carbohydrate metabolism. This appears to be furnished by the cells of the islets of Langerhans

The effects of complete removal of the pancreas on metabolism are as follows The percentage of sugar in the urine is very large, even when fasting, with carbohydrate food the carbohydrates leave the body as dextrose, in protein diet the sugar rises and falls with the nitrogen, and with fatty foods there is an increase in the quotient (Schäfer) De Mayer states that in animals without a pancreas there is an increase in the permeability of the kidneys

The hyperglycæmia which precedes the glycosuria is brought about by conversion of the liver glycogen into sugar, which passes into the blood

Schäfer assumes that the islets of Langerhans produce an internal secretion which affects metabolism in such a manner that there is no undue accumulation of sugar in the blood, and he proposes to call this hypothetical substance 'insuline' He suggests that there are three possible ways in which this can be brought about first, the active agent may be a glycolytic ferment, and may be the source of that ferment which is known to be present in blood second, it may be of the nature of a kinase, the function of which is to convert a pro-ferment into a ferment, or it may be a "chalonic autacoid,"* which tends to
lates

* That is to say, a hormone which inhibits not ~

prevent the formation of glucose from glycogen. Schafer considers that the hypothesis of an inhibitory agent affecting carbohydrate metabolism is probably the correct one

The interrelation of the pancreas and other of the internal secreting organs, and the effects of extracts of these in producing glycosuria, is interesting and important The injection of adrenalin into the blood-stream produces glycosuria, so does brushing the pancreas with adrenalin, stimulating the sympathetic (the splanchnics), and puncture of the medulla The hyperglycæmia following injection of adrenalin is produced immediately, and, moreover, it occurs in depancreatised animals and in cases of diabetes in man It has been shown, however, that adrenal glycosuria can be prevented by extracts of the pancreas or by pancreatic juice

Loewy states that adrenalin dropped into the eye of a depancreatised animal causes dilatation of the pupil, which does not occur in normal animals

Removal of the thyroid tends to prevent most forms of glycosuria, while removal of the parathyroids has the opposite effect 'It may be that the increased tolerance to sugar, which is associated with diminished activity of the thyroid, the posterior lobe of the pituitary, and the medulla of the suprarenals respectively is brought about through the effect upon the pancreas' *

We are not concerned here with the digestive properties of the pancreas or the intestine, except in so far as they encroach upon the study of the internal secretions, we shall, therefore, omit any discussion upon the pancreatic digestive juices and their relation to those secreted from the intestine

* "The Endocrine Organs," p 131

To summarise, then, the primary function of the pancreas is digestion, in the course of which it comes into relation with other of the internal secretions, primarily that of the duodenum The pancreas is in opposition to the secretions of the chromaffin tissue, of the thyroid, and the pituitary, but appears to be related to the parathyroids in another manner, as removal of the latter glands assists glycosuria The pancreatic secretion is concerned in the utilisation of sugar by the body, and enters into relation with the liver in so far as the conversion of glycogen is concerned

## The Thymus.

The thymus gland develops comparatively early in intra-uterine life (about the third month) attains its greatest size soon after birth and thenceforth gradually diminishes until in adult life only the shadow of its former self remains

In structure the gland consists of a fibrous capsule sending trabeculæ between the lobes which carry the blood and lymph vessels The follicles of which the gland is composed are polyhedral in shape, and composed of lymphoid tissue Scattered in this tissue are the characteristic bodies called the corpuscles of Hassall consisting of a nucleated centre surrounded by flattened epithelial cells These latter develop from the pharyngeal mucous membrane, and resemble the epithelial nests sometimes seen in neoplasms Nucleated red corpuscles polymorpho-nuclear cells, and coarse granular cells, are found in the thymus, while various substances can be extracted—such as xanthine adenine, and leucine The main substance found in the cells is proteid particularly nucleo-proteid

The thymus undergoes retrograde changes after puberty, the glandular portions being largely replaced by connective tissue; in instances when this retrogression fails to take place, all the lymphoid tissue of the body tends to be unduly developed, the condition receiving the name of status lymphaticus The thymus consists of two lobes, each composed of a cortex and a medulla

It is believed that this gland is concerned in the formation of the white cells of the blood, a suggestion first made by Beard, and the structure of the gland closely resembles that of ordinary lymphoid tissue and spleen There are, however, no well-defined cells to which could be attributed internal secretory functions For this reason, therefore, the place of the thymus among the organs of internal secretion is not as assured as that of some other glands

The relation of the thymus with the gonads is especially interesting when one considers that this gland is essentially a temporary organ, and that its decline is correlated with the rise into activity of the organs of sex It has been shown that castration causes delay in thymic atrophy, and that, experimentally, removal of the thymus is followed by a rapid growth of the testicles Again, observations show that the thymus tends to persist, in cases where the thyroid is atrophied or its secretion deficient, but it has been stated (Ord and Mackenzie) that the gland is constantly enlarged in Graves' disease

Injection of extracts of thymus and the results of thymus administration in the laboratory are stated to have no specific effects, but some observations from the physiological standpoint are interesting, and possibly throw some light on the success which has attended some of the clinical trials Tadpoles fed

intravenous injection produces a fall of blood-pressure followed by a rise, an increase in contraction of the uterus, and a flow of milk In the male, marked results follow extirpation of the pineal—a more rapid growth of the body, with premature development of the testicles and of the secondary sexual characters Sexual precocity has been observed in boys who have been found to have a tumour of the pineal (but this is not always the case), but such patients, moreover, have been found to have a large interstitial organ (cells of Leydig) These symptoms have been attributed to hypopinealism (Schafer); on the other hand, it has been stated that feeding with pineal extract is followed by precocious sexual development Adiposity has also been noted in connection with tumours of the pineal gland, similar in distribution to that seen in cases of hypopituitarism

It must be admitted, however, that no conclusive evidence has so far established the functions of the pineal gland Formerly, it was regarded as a vestigial remnant, a relic of the third eye Although it is probable that it exerts some influence in the endocrine balance, we are unable to say in exactly what direction

## CHAPTER III

## THE PRINCIPLES OF ORGANOTHERAPY

BEFORE commencing the study of organotherapy, and the various extracts which contribute to its application, it might be useful to consider the principles which underlie this branch of therapeutics. For, while certain organic extracts are established as methods of treatment, other preparations are utilised without the same certainty which characterises the first group.

Harrower, in his book on practical hormone therapy, divides what he calls "the availability of hormone action" into four groups: "substitution therapy," where a missing hormone is assumed to be the cause of the disorder, "supplementary therapy"—the augmentation, directly or reflexly, of a presumed deficiency, "specific physiological therapy"; and "empirical therapy." Into one of these four groups the exhibition of an organic extract will fall.

Let us now enquire into the rationale of organotherapy in detail. To take, as a first example, the utilisation of thyroid extract. This substance has found a wide utility in the treatment of major and minor degrees of thyroid insufficiency. Its dose is accurate—or perhaps it would be better to say the range of its dosage is well understood—and the reaction to be expected from its administration is known. It is coming daily into fuller usage, and is

tending to replace inorganic and vegetable drugs in the treatment of certain disorders.

Using extract of thyroid to illustrate the four bases of organotherapy, in cretinism, the exhibition of the extract would belong to Group I, whereas in myxœdema it would belong to Group II

One of the cardinal signs of deficient thyroid is the subjective sensations of cold of which these sufferers complain. Now, the administration of thyroid extract in small doses frequently ameliorates this symptom It is possible, even where there is no reason to assume a deficiency in the secretion of this gland, to improve the circulation by administering thyroid extract in this instance purely for its "specific physiological effect" Such treatment would belong to Group III

Lastly, empirical therapy consists in the prescribing of an extract without the support of physiological knowledge. I suppose this type of prescribing is found most frequently in that large group of cases coming under the heading "functional"

Here we have a syndrome—*i e*, a collection of *symptoms—the diagnosis of which is concluded* by some such terms as "neurasthenia," "nervous debility," "overstrain," and so on There are, perhaps, no definite physical signs to indicate which, if any, of the internal secretions is at fault Rather in desperation, an organic extract or combination of extracts is prescribed, and the doctor (and his patient) awaits results. Or, relying upon what Leonard Williams calls "a mitrailleuse," a combination of *extracts is decided upon, in the hope that one at least* of the constituent elements will hit the mark.

This form of prescribing is not as evil as it sounds, and for two reasons with certain exceptions the

its action may deserve to be included in the term "empirical" Those who are not enthusiastic on this branch of therapeutics prefer to class most of the results under this latter heading; or to attribute its undoubted successes to an even less tangible agent, suggestion, which is singularly like the conclusion reached by the learned lecturer at a psychological meeting, that he believed the medical psychologists present, who had been discussing their own methods of curing their patients, achieved all their results by suggestion

It is, of course, a matter of relatively small importance in an individual case to ascertain under which heading the treatment should be classed; but, in practice, it is well to keep clear in one's mind the basis upon which one is ordering any line of treatment. For this reason the preceding chapter has given a brief account of the physiological principles of the endocrine organs, in order that the reader may understand what effects follow the experimental administration of the various extracts It must be borne in mind, however, that factors, impossible to estimate with entire accuracy, are always present in dealing with the living subject, and that these factors are infinitely less to be reckoned with in the laboratory. We have already referred to the psychical element, and this, of course, is a factor of the greatest importance in any clinical work, it matters not of what nature

I am not aware, however, that it enters more largely into organic than it does into inorganic therapeutics The polypharmacy, which is mercifully now a thing of bygone days, may certainly be accused of availing itself of the help to be afforded by "suggestion"

The physical factors which have to be reckoned

with in estimating the valency of organotherapy are numerous, and impossible to enumerate with accuracy We are quite unable to say for example, that a preparation will always be potent, however carefully it has been prepared, neither can we tell in every instance whether reaction to a pluriglandular preparation is due to a single element, which has out-balanced the others, or to the combined effects of all the ingredients In this dilemma we are analogously placed to the physician with the half a dozen or more inorganic extracts in his prescription

It must be admitted therefore, that much of the prescribing of organic extracts now proceeding is without a proved foundation, but it is, nevertheless not entirely speculative An example of this is extract of bile This substance is a laxative in small doses—a purgative in large We may prescribe this in cases of constipation without proof that its exhibition falls definitely into any of the groups we have outlined Even so, it is at least as good as aloes tridin cascara, colocynth *et hoc genus omne*, always provided it is as efficacious

Hallion has drawn attention to the stimulating action which an extract exerts upon the organ secreting that extract I xtracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time When the organ is insufficient, it is conceivable that this influence augments its action and when it is injured that it favours its restoration' * A belief based upon such a statement as this supports us when we order thyroid extract in the hope that its use will not have to be continued for the rest of the patient's life It is con-

* This has been called ' …mostimulative organo-therapy'

ceivable, even likely, that an organ might be shamed into adequate work, by the importation into the system of outside help. It is not likely—in fact, we have proof of the contrary—that the organ so treated would go on strike!

Another, and quite different aspect of the organo-therapeutic administration is what I have termed its "antagonistic action." Here an extract is employed to neutralise an excess of the secretion of another organ, and the decision is supported by physiological research. Assuming, for example, that, whatever the primary cause, there is a condition of hyperadrenia present, it should be possible to restore the hormone-balance by means of its physiological antidote. Whether such an antidote can be found in extracts of the islets of Langerhans remains a question which cannot be answered here. Experience in intangible endocrinous disturbances has convinced the present writer that a wide field of utility lies in front of this aspect of organotherapy.

Although a wider knowledge of the pathology of the disorder has convinced us that it is unsound, for some years extract of the adrenals was much vaunted by many authorities as a useful remedy in Graves' disease. This was an example of the "antagonistic" action to which we have just referred, as it was believed that the thyroid was the villain of this particular piece, and that its wiles could be antagonised by the aid of adrenal extract.

Another branch of organotherapy, more direct in theory, which has been followed by pioneers in this branch of therapy is by means of extracts of the alimentary tract. It has been argued that the rational treatment of such disorders as "indigestion and constipation" consists in tho administration of

extracts of the gastric and intestinal glands. Here we are evidently up against a more difficult problem than might at first appear, for many factors are concerned in these disorders, and the student has to ask himself, what is the basic cause, and is the administration of such a preparation as "secretogen" likely to get to the root of the trouble?

Nevertheless, this is yet one more way in which organotherapy can find an opening, and inasmuch as the part to be treated consists of the absorbing surfaces (in so far as treatment *per oram* is concerned), it would seem probable that we should have a good prospect of success. It must be remembered, however, that to reach the intestine the extracts have to pass through the stomach, and that organic extracts are liable to be acted upon, as indeed are inorganic, in their passage through this viscus. This can, of course, be overcome, and in a subsequent chapter when dealing with the therapeutic aspect of gastric and intestinal extracts we shall refer in greater detail to this question.

A wider variation still of the same question is raised when we consider the subject of intestinal stasis and alimentary toxæmia. Here, again, we find a field for the development of organotherapy—a field which promises well as our knowledge becomes more exact. It is certain that some, at least, of the internal secretions are concerned with the defence of the body against invasion by bacteria and their products. The thyroid is unquestionably important in this connection; notice its enlargement in conditions showing evidence of chronic alimentary disturbance. It is no exaggeration to say that many patients who were formerly regarded as suffering from Graves' disease are shown by modern metho

of diagnosis to be the victims of an infection from the bowel. Thyroid extract has been termed the "physiological digitalis", it is unquestionably of use in some cases where we were formerly taught not to use it—for example, cases exhibiting tachycardia where this is dependent upon alimentary toxæmia. It is believed by many that the adrenals and thyroid glands stand between the cells of the body and infection, and that hypoadrenia is often the outcome of slow but constant toxicity. Certainly many patients suffering from obvious poisoning present on examination signs indicative of adrenal exhaustion. It is obvious that the most reasonable method of combating this is by the administration of extracts of the gland or glands presumed to be at fault. If the thyroid and adrenals are over-acting to protect the body, the signs of over-acting, such as tachycardia, should not be checked by inorganic drugs, unless the symptom itself is dangerous to life; any more than a febrile attack should of necessity be attacked by "febrifuges," if we assume that the purpose of the fever is to increase combustion and excretion, and to eliminate the toxic agent. On the other hand, it might be helpful, even while the signs of hyperthyroidism are present, to prescribe small doses of thyroid extract for this would assist an agent which must be regarded as beneficial. When the pendulum swings to the other extreme we have all the signs of hypothyroidism, hypoadrenia, or hypopituitarism. Here, indeed, there is a very clear indication for the administration of organic extracts, either singly or in combination.

It is very remarkable to see patients in whom the signs of hyperadrenia are marked, improve in every way after a febrile attack. Several such instances

have come to the notice of the present writer It is possible that these are fundamentally toxic, and that the fever destroys some toxins by increasing the patient's resistance

Very few actual facts have been established as to the chemistry of the internal secretions, beyond those outlined in the preceding chapter, but many theories have been elaborated as to their action and interaction Von Poehl believes that the chemical action of such substances as thyroidin, adrenalin, spermin, etc, is in the nature of katalysators—i e, agents which can influence bodily metabolism If katalysators were not present in the body, the temperature of the body would be insufficient for the chemical changes necessary to life Spermin is regarded as a katalysator, and adrenalin-glycosuria is considered by von Poehl to be due to this reducing process Another example of the chemical regulation of the body is that shown by exercise Here the increased production of carbon dioxide by the muscles leads to increased activity of the respiratory centre resulting in a great increase of respiratory movement This is an example of a chemical regulator instances of which are evidenced in the secretions of a great many of the bodily tissues Kreatin, formed by the muscles, increases gastric secretion, this action closely resembling those of the endocrine glands themselves The action of the secretion of these organs and the reacting organ is given on page 42 in a table by Starling modified by Langdon Brown *

It will be obvious that these are a few only of the chemical products of the body which act and interact with the products of the organs but they include those glands about which the physiologist can tell us most

* "Physiological Principles in Treatment," p 3

| Origin | Hormone | Reacting Organ. |
|---|---|---|
| Thyroid .. .. | Iodothyrin | Nervous system, skin, etc |
| Suprarenals .. | Adrenalin | Sympathetic nervous system |
| Pituitary body . | Pituitrin | Plain muscle, etc |
| Stomach (pylorus) | Gastric secretion | Stomach (fundus) |
| Duodenum | Secretion | Pancreas, liver |
| Pancreas .. | Pancreatic juice | Intestine |
| Ovaries .. .. | Pancreatic juice | Uterine mucous membrane and mammary gland |

Keeping this table in front of us, we can point to several facts which will help us in the study of the principles of organotherapy Thyroid extract stimulates the circulation and the nervous system, raises the bodily temperature, promotes general nutrition more particularly that of the epidermis and subcutaneous tissue, and increases elimination, this latter effect being due to diuresis and increased loss by nitrogenous waste In subthyroidism we see an individual with a subnormal temperature, slow pulse, sluggish circulation, harsh, dry skin, deficient and lifeless hair, and constipation The effect of administering thyroid extract to such a patient is to stimulate the reacting organs, and to exert the homostimulative action described by Hallion If the extract is given in small initial doses, and gradually increased, the temperature is raised, the pulse-rate will increase and many of the subjective sensations (hypothermia etc ) will be relieved

It must be remembered, in this connection, that the most primitive forms of life respond to chemical

messengers, and that a nervous system is a subsequent development It is only to be expected, therefore, that the earlier, although slower method of intercommunication between the various organs of the body is apt to be overlooked in favour of the more brilliant and speedy method—namely, that afforded by the nervous system The hormones of the body are well termed the regulators of metabolism; the problem in front of the clinician is, how to supply missing or deficient hormones in such a manner that they neutralise the harmful effects of such deficiency We are, unfortunately, far from the desired stage at which we can diagnose a deficiency of one hormone as being the root of a disorder, and supply this in absolute certainty that it will replace the deficiency, and remove all the symptoms of the disorder As Starling says "If the mutual control of the body be argely determined by the production of definite hemical substances in the blood, the discovery of the nature of these substances must enable us to interpose at any desired place in these functions, and by this means to acquire an absolute control over the working of the human body"

This summarises the goal at which organotherapy is striving to day By an intelligent study of the bodily changes which are noted in correlation with known changes in the internal secretions, workers in this field are endeavouring to show that certain disorders are constantly associated with alterations in the hormonic balance The next step (for this work to be of practical value) consists in finding whether it is possible to administer those substances (hormones) manufactured from the glands of animals to the human subject, with the reasonable expectation that they will be absorbed, and will influence the

preparation might render one extract more easily assimilated than another.

All these points have to be considered when we are discussing the availability of hormone action; and it is just as harmful to condemn on insufficient data as it is to claim successes upon inadequate evidence

## CHAPTER IV

## THE THYROPARATHYROID APPARATUS

We have already referred to some points in the physiology and histology of the thyroid gland In this chapter we propose to outline some of the modern views on the function of this gland and its neighbours, the parathyroids, in order that the rationale of thyroid therapy, which is dealt with in the following chapter, may be better understood The history of our present knowledge of the thyroid gland dates from 1859, when Schiff showed that experimental removal of the gland produced convulsions and death This result was confirmed by Kocher, who reported a state of exhaustion with muscular weakness, œdema, pallor, and thickening of the subcutaneous tissues to follow on thyroidectomy He gave the name "cachexia strumipriva" to this condition Subsequent researches have thrown some light on this earlier work, for Horsley in 1885 working with monkeys described symptoms analogous to those just referred to In addition to these, the intelligence was diminished, there was vertigo, attacks of syncope and tetany amounting sometimes to tetanic convulsions

Horsley and other observers noted that the symptoms following thyroidectomy were most severe in carnivorous animals less in man and monkeys, less still in ruminants, and absent in rodents and birds This was subsequently explained by an anatomical discovery made by Gley, that in the rabbit two of the

parathyroids were situated below the thyroid, and therefore escaped removal; whereas, in the dog, all four parathyroids being embedded in the substance of the thyroid are almost certain to be removed in the operation of thyroidectomy. The same observer pointed out that removal of the thyroid alone does not cause death, but removal of all the parathyroids produced the symptoms above described and the fatal issue

This, then, appears to show that the parathyroids have an intimate connection with the nervous system, and it has been suggested that they secrete a hormone the function of which is to destroy toxins, which, when left unneutralised, produce tetanic convulsions We shall return to this question again

### Removal of the Thyroid Gland.

It has been shown that removal of the thyroid gland by itself produces symptoms of disordered metabolism, which vary with the age of the animal. Broadly speaking, these are as follows in young animals there is retardation or cessation of growth, and there is atrophy of the genital organs, while the abdomen becomes enlarged and pendulous In all animals of whatever age certain changes are noted after removal of the thyroid, although death does not necessarily follow The skin becomes coarse, thick, and loses its elasticity, or hard and swollen, while the hair loses its gloss or falls out The temperature becomes subnormal and tends to continue falling, oxidation and the respiratory exchange is diminished, and anæmia is marked This condition becomes more accentuated, and the animal may eventually die.

Another fact of importance is that removal of the thyroid tends to lower resistance to infection

It has been shown that these symptoms can be controlled, at all events temporarily, by grafts of thyroid tissue, or by injections of an aqueous extract of the gland Grafts are now made of small pieces of the gland, and while they function, the symptoms characteristic of "cachexia strumipriva" do not supervene This is strictly analogous to the clinical observation first made by Murray, that the myxœdematous state can be controlled by extract of thyroid gland given by the mouth

From what has been said, it will be obvious that the thyroid secretion is concerned with the general metabolism, and that its absence from the bodily economy results in retention of products which should be eliminated This secretion is concerned with the elimination of nitrogenous products, and is necessary for adequate respiratory exchanges to be maintained

It is established, therefore, that the thyroid is a secreting organ, that the secretion reaches the lymph-stream direct, that the colloid substance of the gland is the seat of the chemical product, and that this can be seen to arise as droplets in the epithelial cells lining the vesicles The substance in question has been called 'thyroiodin' and is rich in iodine and nitrogen It varies in amount in different animals, and indeed in herbivora appears to be absent altogether Its part in regulating the bodily functions has been shown, first, by the results of extirpation, secondly, by the symptoms of myxœdema.

## Removal of the Parathyroids.

In contradistinction to the effects of thyroidectomy, removal of the parathyroids proves rapidly fatal The characteristic feature noticed in animals who have lost these diminutive glands is tetanic spasms and paroxysms, which last until death In some instances the attacks are epileptiform in nature, with foaming at the mouth, violent muscular contractions, and death from spastic immobilisation of the thoracic muscles There is marked dyspnœa, the respirations rising to 100 a minute The temperature is subnormal, except during the convulsive seizures There is a deficiency of oxygenation, with cyanosis The pulse rate is slowed, except during the attacks, when it becomes extremely rapid There is anorexia, vomiting, diarrhœa, and extreme thirst The urine is much less than normal and very toxic, albumin and sugar being often found

It is difficult to form a clear opinion as to the functions of the parathyroids, as there exists much controversy not only on this aspect of the glands, but even upon their anatomical position It is stated that they occur in some instances in positions other than those usually recognised—*e g*, they may be attached to thymic residues, accessory thyroids, or lymphatic glands, and that they escape detection

The two views as to their function may be summarised as follows

1 That their purpose is to supplement the work of the thyroid This view is supported by the fact that life can be carried on even after *thyroidectomy*, the parathyroids appearing to take the place of the thyroid

2 That they are functionally independent of the thyroid

Experiments have shown that all the effects of thyroidectomy can be produced by removal of all the parathyroids, leaving the thyroid intact, also that, although the parathyroids hypertrophy after removal of the thyroid, they do not take on the histological structures of the latter

It must be remembered that in experiments upon the parathyroids it is extremely difficult to make certain that all the parathyroid tissue has been removed The view most generally accepted is that the parathyroids are separate structures, and are functionally independent of the thyroid With regard to the function of the parathyroids, it would appear, from the effect of parathyroidectomy, that this is primarily to destroy toxins which have a selective action upon the nervous system The blood of parathyroidectomised animals has been found to be toxic when injected into normal animals, the urine has likewise been shown to be toxic, and Koch found methylguanidin, cholin, neurin, etc, to be present after this operation It is stated that the liver shows degenerative changes

Injections of parathyroid extract have been found to neutralise the convulsions after thyroidectomy, Vassale, however, has shown that the same effects can be obtained by injections of thyroid extract

Certain observations bearing upon the tetany caused by parathyroidectomy appear to indicate that the administration of calcium salts tends to diminish the violence of the convulsions That the internal secretions have an intimate relation to the calcium metabolism of the body has been known for a long time, and it has been suggested that the hyper-

excitability of the nervous system which follows parathyroidectomy is due to the withdrawal of calcium from the body *

## The Modus Operandi of the Thyroid Secretion.

Beebe says "The physiologically active portion of the gland secretion is a protein substance containing iodine in a specific organic combination" The point of importance is that the thyroid secretion contains iodine, and that in the cells of the thyroid are found nucleo-proteid, globulin, and albumin The secretion of the thyroid has been called an "iodised globulin"

The question which we must attempt to answer here is, In what manner does the thyroid affect metabolism, and what are the means by which these effects are brought about ?

Sajous, whose large work on the subject of "The Internal Secretions" deals so fully with this problem, has definite views on the mode of action of the thyroid † Briefly his views are that the thyroid acts as an "oxidation activator" through its action on the phosphorus of the cells of the body He says "The iodine in organic combination which the thyropara-thyroid secretion contains renders the phosphorus

* Many analogous observations have been made on the part played by calcium salts in health and disease It was suggested by Leduc that there is an increase in the excretion of calcium in neurasthenia, and perhaps this would account for the hyperexcitability of the nervous system so characteristic of this disorder It is largely speculative in the present state of our knowledge, but a very interesting subject to investigate See also Leonard Williams—"On Arterio-sclerosis" *Lancet* 1914, i, 815

† "Internal Secretions and Principles of Medicine," Eighth Edition, chapter iii, vol i

of all tissue cells, and particularly their nuclei, more prone to undergo oxidation by the adrenoxidase of the blood." He stated in an earlier edition of the same work that in his view the thyroid secretion produced its effects in part through the adrenals In 1903 he suggested that the thyroid secretion directly or indirectly increased the adrenal secretory function "The thyroid product is an 'iodised globulin' . . . the globulin being the albuminous constituent of hæmoglobin—i e, adrenoxidase" This author believes that the great activity of the thyroid as an oxidising agent is due to the combination of a ferment (adrenoxidase) "The thyroid and parathyroid secretions ultimately reach the superior vena cava, and are carried to the pulmonary alveoli, where they combine and are taken up by the red corpuscles, along with the adrenal secretion" Again, "The thyroparathyroid constituent of the hæmoglobin enhances oxidation by increasing, as a ferment, the vulnerability of the phosphorus, which all cells, particularly *their nuclei, contain, to oxidation by the adrenoxidase* in the blood"

It has been pointed out that iodine (and consequently thyroiodin) causes excessive elimination of phosphates and phosphoric acid, and also that there is a relation between the thyroid extract and the phosphorus content of the body, large doses of the extract causing excessive phosphorus elimination (shown clinically by tremor, tachycardia, etc), there being a great decrease in phosphorus elimination where thyroidectomy has been performed

Sajous believes, therefore, that the increased combustion of the body due to activity of the thyroid owes its origin to the presence of the activated thyroid secretion (thyroiodin + adrenal secretion =

thyroidase), and that this is able to act upon the phosphorus of the cells, causing an increased elimination

I have quoted at some length from this author, as he suggests an acceptable theory as to the *modus operandi* of the thyroid. All clinicians are familiar with the effect which extract of the thyroid gland has upon tired, obese, hypothermic subjects; but it is not an easy matter to describe how the results achieved by thyroid therapy are brought about. Langdon Brown says that the occasional failures of this extract to ameliorate myxœdema may be due either to the fact that in elderly persons iodothyrin appears to have less effect, or to the fact that it is not always possible to administer an adequate dose to these subjects, as they are more prone to develop toxic symptoms than the average person

Thyroid extract has been prescribed in skin affections—mainly of the chronic type—and good results have been reported by many observers Sub-myxœdema is associated with a lymph stasis, and, it is believed, with a condition of subinfection, or perhaps it would be more accurate to call it a condition of diminished resistance to infection Benefit in affections of the skin would, therefore, be due to the amelioration of either or both of these abnormalities

The colloid in the thyroid gland increases after ligature of the bile-duct (Langdon Brown) If this is a defence against intoxication by bile-salts, the administration of thyroid extract is indicated in all cases where there is biliary stasis or obstruction. It has been given in jaundice and pruritus ani with good results

So far the reader doubtless will be struck with the "detoxicating" powers attributed to the thyroid,

but he will no doubt admit, after hearing the evidence, that there is a real background for the favour with which the theories dealing with this internal secretion have been received

It has been suggested that the thyroid secretion is polyvalent—that is to say, is a compound secretion consisting of several hormones, which differ in their action one stimulating the heart, another the sweat glands, and so on. Although this is a fascinating theory, it hardly seems necessary to postulate such a theory, when we consider that the presence of toxins can be assumed, if not demonstrated, in most cases showing thyroid excitability In some instances it would seem as if the primary cause of the disordered metabolism is to be found in the bowel, the thyroid reacting in defence of the body and showing (for a time, at least) an over-action As the accumulated secretion becomes used up, the supply of thyroiodin *at the disposal of the body becomes exhausted, and a* condition of hypothyroidism may result If such a sequence of events occurs we shall see that the syndrome called Graves' disease can be explained by a succession of over and under-activity of the thyroid, one state supervening upon the other, not, as has been suggested, both being present at once

Many of the disorders in which thyroid extract has been prescribed depend for their causation upon an obvious toxic agent Indeed, it might fairly be said that in all morbid states of the body, where there is evidence of retention of waste products—diseases ranging from epilepsy to rheumatoid arthritis—thyroid therapy has been tried, and very often with success A statement such as this suggests that the extract has become a nostrum, blindly used with infinite faith But this is far from being the

case, as patient investigation has proved that athyrea is found to be associated with a diminished excretion of the end-products of the metabolism, and, moreover, that excretion can be increased by the administration of thyroid extract Sajous explains this and the kindred phenomena of thyroid therapy on the ground that "it renders the phosphorus of all tissues, and all free substances, such as bacteria, wastes, toxins, etc, containing phosphorus, more inflammable or sensitive to the action of the oxygen in the blood" By regulating the dose administered, we can advance or retard the metabolism of the patient, and produce a degree of elimination in proportion to the dose presented

## CHAPTER V

## DISORDERS OF THE THYROID SECRETION

We have referred in the previous chapter to the signs of thyroid deficiency Before describing in detail the disorders in which extract of the thyroid has been proved to be beneficial, we will describe the physiological effects which follow administration of this extract

A rise of temperature is noted, which is more marked in cases where the morning and evening temperature is consistently subnormal This is attributable to the increased oxidation resulting from the thyroid medication, and is accompanied by increased elimination of nitrogenous products, and by diuresis There is a tendency for the pulse-rate to be increased, but there is no augmentation of the force of the heart-beat There is also a loss of weight, due in part to the dehydration of fats and the diuresis.

Subsequently the appetite returns, there is a feeling of well-being, and the mental powers of the patient improve

These effects, of course, all depend upon the dose employed, the length of the treatment, and other factors, such as the age of the patient, the amount of exercise taken, and so on

Thyroid extract " heightens the processes of waste and repair " Hertoghe, who has made an exhau.. study of the signs and symptoms of thyroid deficien

attributes many of these to infiltration of the part concerned: thus, the nocturnal enuresis he believes to be due to a thickening of the mucous lining of the bladder, an analogous condition to the development of adenoids, while the slow mental powers, the vertigo and tinnitus, the constipation, etc., are to be regarded as due to the same cause

The resemblance of these abnormalities to the features which characterise senility is far too close to be overlooked; so that we may regard the signs of hypothyroidism as being a foretaste of a premature senility Léopold-Lévi, in describing the slight form of hyperthyroidism which sometimes accompanies thyroid deficiency, refers to the "syndrome of persistent juvenility"—a contrast to the clinical picture typical of hypothyroidism.

The administration of thyroid extract tends to improve symptoms dependent upon sluggish circulation and the consequent local engorgements Many cases have been reported which show that nocturnal enuresis, slow mental development, and stunted growth, can be remedied by thyroid extract Suffice it to say, at this point, that the field open to thyroid therapy is daily widening, as we know more of the function of the thyroid secretion and its place in the bodily harmony

We may once more emphasise, then, that this secretion is concerned in regulating the metabolism of the body and in aiding elimination by its effect upon the metabolic activity of the hepatic, intestinal, renal, cardiac, and cutaneous systems

Sajous divides the conditions in which thyroid extract may be utilised into five

1 In diseases due to slow destruction of toxic wastes, as shown by its action in tetany, epilepsy,

eclampsia, disorders of menopause, asthma, chronic rheumatism, migraine, and also by those due to slow oxidation of fats, as in obesity

2 In diseases due to lowered nutrition of all tissues, including the bones

3. In disorders due to lowered nutrition of the muscular elements

4 In all cases where the processes of repair or absorption are deficient

5. In infectious diseases, owing to the increase of auto-antitoxin, as shown by its action in the early stages of tuberculosis

We will now study some of these disorders in a little more detail

## Cretinism.

Cretinism, or infantile myxœdema, is a disease marked by defective development, stunted growth, thickened lips and tongue, flattened nose, and more or less imbecility The dry, scaly and pale skin, the puffy face, and the "jelly-like swelling" of the subcutaneous tissue, are all characteristic The disease may develop *in utero*, but it is manifest in the early months of life by the features just described, and by an appearance of senility which these children show

The features which we have come to associate with deficient metabolism are present—the thickening of the integument, the dull, "lifeless' hair, the carious teeth, and the general mental apathy Two types of cretinism are described endemic cretinism, occurring in special localities, and attributed to some abnormality in the water, and sporadic cretinism, which occurs in isolated examples, and is usually a sequela to an acute illness, such as a fever

In both varieties the symptoms are the same, and it is recognised that we are dealing with arrested physical and mental development due to a deficient or missing hormone.

The improvement which follows treatment by thyroid extract is very marked The period at which the disorder has commenced, and likewise the amount of *mental and physical delay in development which* is present when treatment is undertaken, have a marked effect upon the progress of the case As soon as thyroid extract is given, however, improvement is usually always manifest, in many cases in a few days to a few weeks' time Growth is resumed, the child commences to take an interest in his surroundings, and if he has hitherto failed to distinguish people from objects, he begins to show recognition of his environment So long as the treatment is continued the approach to normal continues, but the patient is liable to a set-back if the extract is not given for any length of time

*Considerable skill is required to arrive* at an accurate dosage The approximation to normal development is delayed, if the amount given is insufficient for the individual case, but, against this, it must be remembered that considerable harm may result if a dose excessive to the requirement of the patient be administered Many authorities believe that a large dose, even if not dangerous, defeats its own purpose by unduly accelerating the processes of waste *A word of warning is, however, necessary,* as serious, even fatal results may accrue from too large an initial dose, and from increasing the dose too rapidly. Whatever the commencing dose, a careful watch should be kept upon the reaction of the patient; the temperature, pulse-rate, and cardiac action all

indicate when the drug is beginning to exert its action.

Many clinicians with wide organotherapeutic experience emphasise the importance of small doses of thyroid, more especially when commencing treatment. The dosage so commonly advocated to-day—of 3 to 10 grains—is far in excess of the limit of safety, and is certain to be too large even for cases showing marked hypothyrea. Indeed, this latter class of patient is unduly susceptible to the action of thyroid, and the initial dose should be smaller than for the majority of patients.

Fractions of a grain should limit the initial dose. Half a grain of thyroid extract is a good initial dose in cretinism, and I think there is no doubt that this is better administered at night so that the patient, as recommended by Murray, rests in the recumbent position after the dose. Such a method is safe, and allows the reaction to be watched. As the extract becomes effective the temperature approximates to or reaches normal. This is a sure guide to the dosage, for once the temperature is up to normal, the dose should not be further increased.

## Myxœdema.

Myxœdema may be regarded as the analogue of cretinism, appearing, however, in adult life. It is characterised by similar features, indeed, the patient may be said to be dull mentally and physically. The skin is harsh and dry, and lacks the smooth surface which is seen in health. The face becomes broad, the nose, eyelids, and lips thickened, while the colour of the cheeks is yellow rather than pink. The eyes

appear dull and the expression lethargic The hands are held in a manner characteristic of this disorder—a manner which has been called "spade-like" The bodily movements are carried out with deliberation, and the reaction to questions is considerably lengthened The tongue is thickened and swollen, and this doubtless contributes to the characteristic speech, which is slow and deliberate, like the movements of the body

There is usually a marked absence of sweating, and the patients feel the cold intensely The nutrition of the epidermal structures all suffer, and the teeth, hair, and nails are brittle and lifeless, the first-named often being markedly carious The hair on the head is scanty, and often consists of a few dull strands; while the eyebrows are conspicuous by their absence

The mucous membranes are often bright red, and nearly always thickened, the lips, in particular, presenting an engorged appearance

The temperature is always subnormal, sometimes markedly so, and the hands and feet are blue and cold to the touch even in mild weather, while the winter is announced by the appearance of chilblains The pulse is slow, in some cases very slow, the blood-pressure low, and the cardiac action weak The bowels are usually costive, the urine of a low specific gravity, with a diminished quantity of urea, but albuminuria is rather the exception than the rule, except in advanced cases

The thyroid gland is either unable to be felt by the finger, or else is only just discernible, but this gland is often difficult to localise accurately even in normal individuals

The post-mortem appearance of the thyroid gland

in a case of myxœdema is striking The gland is much smaller than usual, and presents a shrunken, fibrous, and structureless appearance On section there is seen a small-celled infiltration of the walls of the vesicles, with much fibrous tissue containing scattered groups of cells *

The administration of thyroid extract is followed by improvement in all the symptoms, but the first change to be noticed is, perhaps, an increase in the patient's energy and initiative, and a loss of weight The temperature approximates more closely to normal, the pulse-rate is quickened, the skin and its appendages become more healthy, and the degree of constipation is lessened During thyroid administration the excretion of urea and nitrogen is heightened, the total quantity of urine passed also being increased A more or less generalised desquamation has been noticed when the extract is first given The length of time during which the treatment should be carried out is quite indefinite, but it should certainly be persevered with for several years

## Submyxœdema.

This name has been given to a condition presenting most of the features characteristic of myxœdema, but the extreme degree of the symptoms of the major disease is lacking—in fact, it is a "young edition" of the former The "spade like" hands, the much thickened lips, and the hairless head, are not seen,

* Two cases in which mental symptoms predominated have been reported by French In one, which died, atrophy of the thyroid gland was found at the autopsy The other was cured by thyroid extract —*Guy's Hospital Gazette*, 1915, 72, 73

but in their place the observer encounters premature greyness of hair, deficiency of eyebrow, teeth which have either been copiously filled or should have been, and a sluggish tendency of mind and body. Constipation is usual, and there are many signs and symptoms of deficient elimination, examples of which are pads of fat in certain areas, stiffness of muscles and joints, and a tendency to headache

Such patients consult a doctor, complaining, it may be, of a lack of energy, undue somnolence, headaches, constipation, or symptoms of mental inertia, and upon examination the signs described above will be observed There are, however, certain well-recognised signs of thyroid deficiency which it is customary to describe

A good deal of stress has been laid upon the "*eyebrow*" *sign, first emphasised by Léopold-Lévi* and H de Rothschild This consists in a sparseness of hair in the outer third of each eyebrow, and is believed to be characteristic of a deficiency of thyroid secretion There is little doubt that it is fairly constantly seen in patients who present other signs of submyxœdema, and that many individuals of this type are vastly improved by the exhibition of thyroid extract

The manner in which the adipose tissue is deposited is likewise typical There is no generalised stoutness, but the patient presents pads of fat, more especially over the scapular region and neck, both in front and behind, the abdomen, and the flanks The extremities may be found to be comparatively slender, or if not, the upper arm and thigh are disproportionately thickened compared with the forearm and calf

The temperature is always subnormal, and if taken

consistently it will rarely, if ever, be found as high as 98.4° This corresponds, of course, with the subjective symptom of chilliness, of which these patients constantly complain The pulse-rate is slow, and rarely reaches more than 60 per minute. Anything from 50 to 60 per minute is usually noted. The blood-pressure is less constant in submyxœdema, but from a number of observations which the present writer has made in patients who have subsequently benefited by the administration of this extract, he is of the opinion that it is usually below normal, but sometimes supernormal As many factors, both endocrine and other, are here concerned, this feature is not of much use in this connection

There is a type of individual, which those accustomed to endocrinological diagnosis at once recognise, presenting features depending upon a deficiency of thyroid secretion, usually of long standing Such a type is often small, with deep-set eyes, round face, prominent abdomen, slow in movement and ponderous in thought When examination reveals a slow pulse, a subnormal temperature, and a dry skin, it is probable that the patient will benefit from thyroid extract

The methods of administration will be discussed in detail in the following chapter

## Obesity.

The state of obesity is one which is often if not usually, associated with an underlying hypothyroidism, either directly or indirectly, through a disturbance of the hormone-balance viâ one of the other endocrine glands concerned with nutrition Unfortunately, the utility of thyroid extract has become

known to the laity, and this knowledge has enabled self-dosing with this drug to be somewhat widely practised, with results which are either bad from the point of view of the obesity, or worse from the point of view of the general health It is difficult to get anyone who is unversed in therapeutics to comprehend that because a drug is efficacious in small doses, it is not necessarily twice as good in double doses, and thyroid extract has been utilised for the reduction of fat in absurdly large if not actually dangerous doses

Obesity is due to deficient oxidation and elimination of fats, and is brought about in many cases by the deficient action of one of the endocrine glands An example of this is seen in the obesity which occurs at the menopause, or after oöphorectomy, and this can often be relieved by the administration of ovarian, thyroid, or pituitary extract In this case, the thyroid acts by taking over from the ovaries some of their work of oxidation

It is not uncommon, moreover, for weight to be rapidly gained after an acute illness, and for this to be accompanied by lethargy, lack of energy, undue fatigue, and some such manifestation of disturbed metabolism as phosphaturia Whatever other treatment is initiated, small doses of thyroid should be given, for this will assist in the oxidation of the fats and the reduction of the weight But the doses must be small, or the result will not be what is expected In all obese cases, perhaps more especially in those belonging to the latter class, the increase in weight has been accompanied by some degree of fatty infiltration of muscles, and in this the cardiac muscle does not escape Large doses of thyroid stimulate the heart, and may well lead to enlargement, if not

to heart-failure, especially if they are persisted in after signs of cardiac embarrassment have become evident

From what is known of the internal secretions and their interaction, it would appear that it is possible to stimulate one hormone by and through another, so far as a common action is concerned, just as it is possible to neutralise the over-action of one hormone by supplying another The thyroid, pituitary, adrenals, and gonads, are concerned, *inter alia*, in the regulation of metabolism and if one of these is removed, as happens after oöphorectomy, one stimulator of metabolism is removed The supply of the deficient hormone or of one extract of one of the other " regulators of metabolism " may be efficacious in neutralising this loss The exhibition of thyroid extract is believed to " whip-up " the secretion of the other regulators, and a similar result accrues from the prescription of the pituitary, suprarenal, or orchitic extract

Sajous goes so far as to state that, with suitable doses of thyroid extract weight can be reduced without the necessity of dieting He says " Such doses do not impose upon the patient the need of modifying his usual mode of living, and his diet need not, unless excessive, be altered ' * The rare disease known as adiposis dolorosa or Dercum's disease, is stated to be amenable to thyroid extract, and Professor Dercum recommends doses from 2½ to 5 grains three times a day

* 'Internal Secretions and Principles of Medicine' vol i p 726

### Toxæmia.

In the first group of abnormalities in which the thyroid is concerned, which we have quoted on page 58, "diseases due to slowed destruction of toxic wastes" are referred to Among these, eclampsia, tetany, epilepsy, asthma, chronic rheumatism, and migraine are mentioned, and these are only some of the morbid states which probably depend upon an underlying toxæmia It has been established that one of the functions of the thyroid is that of a filter or "vital antiseptic," to help in the destruction of toxins In many cases of toxæmia, a swelling of the thyroid can be seen, in other patients, equally obviously toxic, the condition of the thyroid is just the reverse, and it is difficult to locate the gland by palpation The explanation of this apparent paradox may be that, with the first case, the thyroid is still able to hypertrophy, and supply an increased quantity of secretion, while in the latter the increased call has resulted in an atrophy of the gland

The association between the functions of the thyroid and toxæmia can be better understood by several factors which are noticed in hypothyroidism The presence of constipation in these subjects would assist in the retention and possible putrefaction of the intestinal contents, with resulting toxæmia Many of the symptoms of hypothyroidism so closely resemble those known to be present in recognised toxæmias, that one might well believe them to be dependent upon an underlying poisoning Bradycardia is well known to be one of the symptoms of toxæmia, and the tachycardia of hyperthyroidism

may be regarded as an earlier stage of the same reaction *

Many writers refer to constipation as a symptom of either thyroid or pituitary deficiency, some of them associating this symptom with headache, anorexia, or indigestion, while they regard diarrhœa as the necessary concomitant of hyperthyroidism It is an established fact, however, that many patients who present a syndrome such as this are benefited by taking thyroid extract

In the view of the present writer, no explanation of the part played by the thyroid in the bodily harmony is satisfactory which excludes its antitoxic power. Further proof of this is obtained by the help which this extract affords in toxic cases, by the fact that where hypertrophy of the gland is present it not infrequently disappears under small doses of thyroid, which fact is readily explained if we realise the above factor Again, Lane, in his work on intestinal stasis, has drawn up a list of symptoms which he believes are characteristic of this condition One of these is atrophy of the thyroid, but as I have pointed out elsewhere, the opposite relation is at least possible—namely, that the stasis is the result of hypothyroidism †

In any case, the thyroid is concerned in the defence of the body, and a condition of partial exhaustion is not uncommon after infections the exanthemata, and lengthy and protracted illnesses By supplying

* In many patients presenting signs of toxæmia, disorders of the cardiac rhythm are evident, and I have often noticed that this condition disappears as the toxæmia improves

† "The Organs of Internal Secretion," Third Edition chapter v, pp 109–110

the extract in suitable doses, the physician is helping nature in the most rational way.

The evidence for prescribing thyroid extract in such disorders as asthma, epilepsy, and eclampsia is steadily accumulating, more especially as the essentially toxic nature of these diseases is being ever more widely recognised Thyroid extract causes increased catabolism, and consequently it throws more waste-products into the circulation Large doses are, therefore, liable to be followed by an increase in the symptoms, and this accounts for the failure of this extract in the hands of some observers, and is an additional argument for small doses of the drug, certainly when it is first prescribed.

## Chronic Rheumatism.

It is believed that the variety of toxæmia known as chronic rheumatism is not only dependent upon endocrine disturbance, but amenable to thyroid therapy. Recent literature on this subject suggests fresh explanations of old etiological factors, and some feasible hypotheses have been formed, some of which go a long way toward explaining this disorder

We have already referred to the evidence of hypothyroidism—the sluggish circulation, and the deposits in subcutaneous tissue, muscles, and joints—and have stated that these can usually be made to yield to thyroid therapy The pathological factors underlying chronic rheumatism are similar in nature, and the ingestion of thyroid produces increased tissue breakdown and elimination

Sajous explains the pathogenesis of chronic rheumatism as follows * Rheumatism is due to the

* *Op cit* pp 730–731

presence in the blood of toxic wastes due to excessive tissue metabolism, which upset the normal activity of the adrenal system. Hyperconstriction of vessels occurs, but hyperæmia of all capillaries (these do not possess a muscular coat), more especially those of the serous membranes and joints, "as a result of the hyperoxygenation of the thyroid apparatus, an accumulation of autotoxic bodies in the blood plasma, and effusion into the joints, serous membranes, glandular elements, etc." By this mechanism he explains the inflammatory lesions, with their predilection for myocardium, pericardium, tonsils, etc. The joints, with their synovial membrane, share in this process, and become swollen and painful, and eventually fibrosis sets in. "While the toxins of various bacteria, *Staphylococcus citreus*, *Micrococcus lanceolatus*, the gonococcus, may be stimulated—especially in individuals in whom this organ is hypersensitive—to provoke acute rheumatism, it is caused in most cases by intermediate toxic waste products which appear in the blood as the result of exposure to cold and the resulting hypocatabolism—the cellular trypsin failing, when the local temperature is below normal, to break down adequately worn-out cell material."*

The above represents the views of this well known authority on the question of the pathology of rheumatism. Two facts important to the treatment emerge if we accept this hypothesis. First, that the diet should be regulated to produce the minimal quantity of "toxic wastes"; secondly, that the administration of thyroid extract should theoretically be beneficial. For years it has been the habit of physicians to cut down or prohibit red meats.

* *Ibid.*, p. 711.

disorder, and generally to regulate the food so that the protein level should be kept low; this practice is obviously sound in the light of our new reasoning. The prescription of thyroid has been attended with excellent results in many cases of rheumatism, rheumatoid arthritis, and allied disorders. The dose should be kept low, and the reaction to this drug carefully watched As is the case in most other conditions in which thyroid extract has been utilised, better results have been recorded by using small doses than by large ones

### Skin Diseases.

Thyroid therapy has been tried in most skin diseases, and its efficacy has been tested in disorders ranging from psoriasis to lupus It is difficult to form a judgment as to the utility of the drug for this class of disorder, but the results are by no means discouraging, certainly in regard to some varieties of dermatoses

Theoretically, moreover, there is sound reason for assuming that thyroid therapy would assist in certain skin disorders, more especially those with an underlying toxic basis The skin and its appendages figure largely in the casualty list when the individual suffers from thyreoprivia, in fact, upon the changes in the skin the diagnosis is somewhat largely based The nutritional epidermal changes seen in myxœdema, submyxœdema, and cretinism, point to the evil effects which follow the withdrawal of this secretion from the blood-stream Reversing this, we may next discuss the beneficial changes which accrue from an adequate supply of this hormone

Cases of scleroderma, associated with small and

other signs of endocrine disturbance, more especially in the direction of delayed mental and physical development.

Now we are faced here with a problem in which the thyroid is certainly not the sole, even if the chief, offender Somewhere in the etiological chain comes the thymus, and secondary to its misbehaviour the gonads *Therapeutically, the thyroid will often work* wonders in such children, producing a healthier and [illegible]

is partly due to the endocrine deficiency which is the common basis of both

*Doubtless, administration of thyroid extract causes* the diminution in lymphatic tissue, particularly when it is adventitious, as in the case of "adenoids and enlarged tonsils" Moreover, in these cases, if treatment could be commenced early enough, thyroid extract and breathing exercises might be a prophylactic treatment, and would certainly be preferable *to the repeated operations which some children have* to undergo

### Nocturnal Enuresis.

It is perhaps exaggerated to say that this condition may be regarded as one of the stigmata of hypothyroidism, as, of course, not only are other causes sometimes responsible, but it is not always ameliorated *by thyroid therapy*

In many cases, however, nocturnal enuresis exists in company with other signs of *delayed and imperfect* development, such as stunted growth, feeble musculature, adenoid growths, flat-feet, or delayed epi-

physeal development Removal of adenoids in such patients does not benefit the syndrome,* but the administration of thyroid extract does so definitely, provided hypothyrea is at the basis of the trouble While it is worthy of a trial in all cases of nocturnal enuresis in children, it is the specific treatment where this condition is accompanied by other signs of thyroid inadequacy

Hertoghe has described this condition at some length, and suggested its underlying pathology There is weakness of control of the sphincter, thickening and desquamation of the bladder mucosa, the latter showing itself by the presence of vesical epithelium in the urine

## Neuroses and Psychoses.

It has been established in recent years that the action of the thyroid can be disturbed either by emotional causes or by physical agents In the recent war many instances where neuroses were combined with a manifest swelling of the thyroid were witnessed and where the gland subsided as the functional symptoms improved We have already seen that the thyroid can and does enlarge in patients who present obvious toxic symptoms

Doubtless in both these instances it is open to argument whether the thyroid was not the primary "starting point" of the disorder but the weight of evidence is in favour of it being secondary to some other causative factor

More psychoses are now believed to have a toxic basis than was formerly believed to be the case, and

* L Williams Lancet May 1 1909

the same theory has been applied to the genesis of epilepsy This being admitted, the utilisation of bromide, frequently in large doses, will do nothing to neutralise the toxicity, but will tend to prevent adequate elimination The fact that some at least of these disorders have been benefited by careful and thorough purgation and hydrotherapy, combined with such help as can be obtained from the extract of thyroid, would appear to support the theory which attributes some of these disorders to toxicity.

It is not possible to describe in greater detail which of the psychoses are toxic and which are due to psychic trauma or other cause, as there are few facts known to guide us in thus discriminating Obviously many functional disturbances are associated with deficient elimination—as shown by a furred tongue, offensive breath, acne spots, malodorous sweat, *et hoc genus omne* (this is, of course, especially true of epilepsy)—and commencing treatment from this standpoint has a good deal to recommend it Our forefathers in physic recognised the toxic element in most disease, witness the almost universal initial treatment—" a brisk purge " Our efforts should be a continuous combating of deficient elimination, rather than a single clearance of the bowel, and in this thyroid extract helps, not only in counteracting toxæmia, but in its stimulating action upon peristalsis As patients suffering from hypothyroidism are always costive, we may assume that this symptom is brought about by the deficiency of this hormone Whether in the future, as our knowledge of the details of organotherapy becomes wider, we shall be able to prescribe a specific extract for the various psychoses, remains to be seen At present there is little doubt that thyroid extract is indicated in certain varieties of the

thyroid appears to be present. In some instances it would appear that this has supervened upon an over-activity. Patients in this class occasionally show evidences of thyroid "wobbling"—that is to say, they present features of under-activity combined with those of over-activity, and some authors think examples of this are more frequently encountered than has hitherto been supposed. "Every time a gland shows pathological hyperfunctions, it will pass through various stages and burn itself out, and will eventually stop functioning entirely. In other words, a Basedow will eventually become a myxœdema. One can, therefore, observe a patient showing exophthalmia, von Graefe sign, tremor, together with putting on weight, dullness, and apathy, where previously he or she was thin, full of excessive energy, etc., this shows the transitory phase."*

At this length of time since hostilities ceased, the physician is coming into contact with cases such as these, and is seeing among pensioners many examples of a deficiency in the thyroid secretion. The signs are often slight, indeed, the closest scrutiny is required to detect small degrees of hypothyroidism. But the languor, asthenia, and difficulties in concentration, of which so many complain, are more often than not helped by the administration of this extract.

In the war cases, it was easier to trace the various factors concerned in the production of the disorder, because the etiological details were clearer, we have, therefore, utilised cases such as these to show how the endocrine system, with its corner-stone, the thyroid, becomes involved. Doubtless, similar factors are present in the functional disorders of civil life.

* "The Little Signs of Thyroid Disturbance," J. H. Leiner, *New York Med. Rec.*, [illegible] [illegible]o. 3.

has to treat, and if organotherapy can help, it will be warmly welcomed as a therapeutic addition

A widely different condition, but one where the etiology is also unknown, is alopecia areata Theoretically, thyroid extract should help this disorder, and it has been tried with a certain success Strandberg reports nine cases of alopecia areata, where the cause appeared to be endocrine Thyroid extract was applied in every case, and in three the hair grew again under thyroid administration.

The stimulating action of thyroid has been utilised in cases of sexual depression, impotence, and debility As there is a reciprocal action between the thyroid and the gonads, there is some basis for this method

## Thyroid Over-action.

At the opposite pole to the condition we have been studying stands hyperthyroidism There is one disorder where this over-action is recognised as being a fundamental part of the disease, and that is Graves' disease, or exophthalmic goitre At one time it was thought that exuberance of the thyroid and consequent hypersecretion was the main, if not the sole, etiological factor Other hypotheses have now enlarged upon this view, and fresh experimental data has lent support to the wider conception of the causation

It is not part of our work to offer a description of the signs, symptoms, differential diagnosis, and treatment of this disease, as these will be found in any text-book of medicine We will, however, briefly discuss certain facts which are of interest, and consider slighter varieties of hyperthyroidism, which offer a wide field of interest to the organotherapist.

symptom of Graves' disease Mackenzie insists that the condition cannot be diagnosed without its presence The cardiac rate is always rapid, and may, in severe cases, reach 120 to 140 per minute The heart is extremely irritable and accelerates on the slightest stimulation, whether physical or psychical The oculo-cardiac reflex is present and marked, and a moderate degree of left ventricular dilatation is nearly always present

This symptom is in keeping with other signs of sympathetic irritability—the sweating, tremors, and dermatographia

### Lesser Degrees of Hyperthyroidism.

In practice it is usual to see patients exhibiting signs which bear some resemblance to exophthalmic goitre, but which are present in a minor degree Some patients have tachycardia, for which no reason is obvious Many cases which during the war were referred to as "disordered action of the heart," or more briefly "D A H," showed other signs of overaction of the sympathetic Hyperthyroidism, which is always associated with the latter feature, may obviously be present in minor degrees, which, therefore, will not show the complete picture we recognise as Graves' disease Mild enlargement of the thyroid accompanied by tachycardia should lead us to suspect that Graves' disease might supervene, and should make treatment imperative When accompanied by the nervousness so characteristic of the major disorder, and by the smaller signs (gastro-intestinal irritability, loss of weight, insomnia, etc), the physician should be warned and insist upon prompt therapeutic measures.

# CHAPTER VI

## THE ADMINISTRATION OF THYROID AND PARATHYROID EXTRACT

### Introductory.

EVERY chapter or article dealing with thyroid therapy should commence with the words "Let the initial dose be small." The next sentence might read with advantage "And keep successive doses small."

There is really only one condition in which doses larger than a grain are ever necessary, and that is myxœdema.* In the majority of the disorders of the thyroid gland, to which reference was made in the last chapter, small doses are the rule. All endocrinologists are convinced of this, and the majority are insistently repeating the warning with which this chapter commences.

If we glance briefly at the therapeutic action of thyroid extract we shall understand better that its administration is accompanied by profound and important changes, even if these are not always stressed by the patient.

The action of thyroid extract is as follows:

1. The metabolism as a whole is augmented and the elimination of the body increased.

* Larger doses have been recommended in one or two other diseases—e.g. Dercum's disease but such doses are comparatively rarely indicated and then only after some degree of tolerance is established.

2. There is a rise of temperature

3 The circulation is profoundly affected, the pulse-rate increases, the excitability of the heart is raised, and there is a liability to arrhythmia.

4 Appetite is improved, digestion is improved, and constipation is lessened

5 There is generally a loss of weight, and if this is produced too rapidly—*i.e.*, by too large initial doses—there is a tendency to restlessness, insomnia, and fainting attacks

6 Sweating occurs, sometimes even from minute doses, and tremors and weakness may ensue unless the dose is regulated with care

The changes occurring during thyroid therapy can best be explained by the hypothesis of Sajous. "It renders the phosphorus of all tissue, and all free substances—such as bacteria, wastes, toxins, etc—containing phosphorus more inflammable or sensitive to the action of the oxygen in the blood As this applies particularly to nerves and nerve-centres (all of which are especially rich in phosphorus), the adrenal centre and, therefore, the adrenals themselves are excited, and the adrenal secretion being the agent which takes up the oxygen of the air to sustain the blood's oxygenising power, the supply of oxygen is also increased All the various phosphorus-laden substances are then not only rendered more readily oxidisable by thyroid extract, but this remedy also provides indirectly the required oxygen. This is not all, however As the functions of all organs are enhanced by this process, the pancreas and the leucocytogenic organs are also stimulated, and trypsin and phagocytes, which are the active destroyers of pathogenic organisms, toxins, and other poisons, are also increased Briefly, under the

influence of thyroid preparations, we have in the blood—and demonstrable therein—all the active agents concerned with metabolism, nutrition, and immunity . . ."*

## Dosage.

In prescribing a course of treatment by thyroid extract, the physician has three staple guides to the regulation of the dosage—namely, the temperature, pulse-rate, and weight These are of more value than the subjective changes reported by the patient, for they are sure guides, both to the etiology and the suitable dosage Where the temperature rises after small initial doses, accompanied by an increased pulse-rate, it is a proof that there is an underlying thyroid deficiency, and that the exhibition of the extract is increasing metabolism Where there is no underlying deficiency, these reactions are not nearly so marked, and I have formulated a maxim for my own guidance in regulating the posology of this drug—" The greater the need appears, the smaller should be the initial dose " I am not here referring to myxœdema, which stands in a class by itself so far as opotherapy is concerned, although the rule of gradually increasing doses holds good even for this disease But I am at present discussing the more delicate and difficult task of prescribing suitable doses for patients suspected of submyxœdema, and the adequate utilisation of the drug empirically

The temperature and pulse-rate, therefore, can be regarded as a guide to the progress of the case Before treatment is commenced, the thermometer will register from 96° to 97°, in fact, I have seen on several

* *Op cit*, vol i, pp 708–709.

occasions a temperature below 95° As soon as an adequate dose is reached it will rise gradually until it reaches 98°; occasionally a supernormal temperature is recorded as a reaction to the drug.

The pulse-rate will show acceleration, and will *normally reach the region of 70 by the time the* temperature approximates to normal.

The weight is paradoxical, or rather it varies according to the type of case under treatment. In broad terms, the victim of myxœdema will lose weight, the sufferer from toxæmia will gain it. The former case affords an example of the specific utilisation of the drug, the latter of its employment in virtue of its action as a "bodily antiseptic" Practical experience with this extract confirms this opinion, and goes to show, as Lane has pointed out with reference to intestinal stasis, that toxæmia is accompanied by loss of weight Thyroid extract has been dubbed "the physiological digitalis" on account of its diuretic power, and in any case when the physician is seeking to increase elimination, the aid of this extract may be involved Large doses, as we have already stated, cause an excessive catabolism, and the patient feels the effect of this The subjective side should always be taken into account, when the question is raised as to the augmentation of the dose of the extract, if the patient complains of fatigue, "sinking feelings," and depression, the dose should not be increased

The dose of thyroid extract, administered by the mouth, is still given in the text-books as from 3 to 10 grains This dose is, of course, far in excess of what is suitable There is no question that fractions of a grain should be the commencing dose, and the prescriber should accustom himself to think of this

extract in terms of fractions of a grain The dose of thyroid extract, therefore, should be considered as from $\frac{1}{10}$ to $\frac{1}{4}$ grain, for an initial dose, and the maximum dose suitable for ordinary usage should be 1 grain, or possibly 2 grains, but never in excess of this

When thyroid therapy was first initiated, it was, of course, for myxœdema, and, as we have already said, this is the one disorder where larger doses are required. This explains the dosage still given, as its utility in the disorders referred to in the previous chapter is of comparatively recent discovery

The present writer has seen unpleasant and even alarming reaction from an initial dose as small as $\frac{1}{2}$ grain, but he has seen more than one case where this extract, prescribed for herself by the patient, was being taken in doses of 20 or 30 grains a day! Its effects were realised by the patient who said she could "never stand these doses unless she stayed in bed all day"

Another point of importance is concerned with the preparation of the extract The prescriber should be quite clear as to whether the extract he prescribes is the whole extract or a dried extract Most manufacturing chemists state that their extracts are prepared from the fresh gland, or if not, they notify the prescriber to the contrary

Thyroideum siccum (B P) is about five times as strong as the extract of the fresh gland The initial doses given above—namely, $\frac{1}{10}$ to $\frac{1}{4}$ grain—refer to an extract made from fresh thyroid gland

### Methods of Administration.

(a) By the mouth
(b) Hypodermically.

*(a) By the Mouth*

The preparations in use for oral administration are powders, tablets, capsules, and the liquid form

There are many varieties of these on the market, and the prescriber has a wide choice of preparations. By far the most widely used *preparation is the tablet.* It is convenient, portable, and its dosage is accurate Also, it keeps longer than a liquid preparation The disadvantage attaching to its use is that it is stated that excessive pressure during manufacture may render the tablet useless

Thyroideum siccum consists of the powdered gland freed from external fat and connective tissue, and purified by petroleum ether It is administered in powder form, but is obviously more cumbersome than tablet and is very little used

The *liquor thyroidei is of no use if more* than a week old, and has, in consequence, a relatively small sale, as the chemist has to obtain supplies for each patient Liquid preparations in the form of elixirs, guaranteed active by their makers, are on the market, and are widely used They are convenient, as they combine with the extract of other glands in the form of a mixture, their dosage can be readily altered, and they are usually palatable to take The efficacy of this form is, in my opinion, undoubted, and I have satisfied myself of the activity of many of the preparations

Another method of administration, *per oram*, is

in the form of gelatine-coated capsules These are made in various strengths, and are a satisfactory method of administration

### (b) *Hypodermically*

Thyroid extract has been given by hypodermic and intramuscular injection, but this method has never been as widely used as the oral As we have already said, thyroid extract is readily absorbed from the alimentary tract, and there is not much point in utilising the hypodermic route, unless in exceptional circumstances Where the digestion is impaired, and where other drugs are being administered, which make it difficult to give this extract by the mouth, this method might be utilised Preparations are manufactured which contain a dosage equivalent to a definite quantity of fresh gland substance

If this method is adopted it is preferable to give the injections not more frequently than alternate days, and to keep the patient in bed on the days the injections are administered

In the case of some other of the organic extracts, the hypodermic or intramuscular route has more to recommend it, but it is the exception rather than the rule to utilise it in the case of thyroid extract

## Important Points in Thyroid Therapy.

There are a few points in connection with the administration of thyroid extract which it will amply repay prescribers to remember

The following are among them

1 Where a single dose a day is prescribed it should always be taken at bedtime, in order that the

patient may have the night's rest between him and *exertion*

2 Both physical and mental work should, so far as is practicable, be limited while the treatment is in progress

3 It is sometimes wise, especially in those cases which appear to react quickly, to make a definite break in the treatment at stated intervals Thus, the patient may take the extract for three weeks, and omit it for the fourth every month; or a fortnight's treatment may be followed by two or three days' rest The condition of the circulation during the rest compared with during administration should be noted as a guide to future doses

4 It is sometimes wise to omit the treatment altogether during the catamenia

## The Parathyroids.

The therapeutics of the parathyroid glands are in a less certain state than those of the thyroid. The condition which supervenes upon removal of these small glands—known as tetany—is some guide to the clinical state in which it is likely to be of use

Parathyreopriva is followed by tremors, loss of flesh, an increase in the calcium metabolism of the body, and if all four parathyroids are removed death ensues If one parathyroid be left, tetany supervenes, but, as a rule, the animal does not die In one patient, whose case is recorded by Hurst, the symptoms came on some time after part of the thyroid gland had been removed at an operation, and it was not until dried extract of parathyroid was administered that recovery began

The parathyroids, it is believed, are concerned as

much as the thyroid with the protection of the body against toxins Sajous, whose views on the thyroid gland we have already quoted, states that we must regard these small glands " . as the essence, so to say, of the whole thyroid apparatus, in so far as its antitoxic properties and its rôle in calcium metabolism are concerned "

There are, however, a number of indefinite clinical states which suggest that the parathyroids are involved in their pathology As an example, long-standing cases of neurasthenia, anxiety neurosis, " post-influenzal debility," and similar conditions bear a somewhat striking resemblance to the state known as " post-operative parathyroid tetany " The present writer has utilised parathyroid extract in some cases of this nature, and, although the material is too scanty at present to speak dogmatically, improvement has certainly followed this administration in several cases

Parathyroid extract has been utilised in paralysis agitans, and it has been stated by one authority that its administration has been followed by marked benefit Such disorders as eclampsia, epilepsy, Graves' disease, and chorea have been treated by this extract, on the reasoning outlined in the previous chapter

The dose of this extract is from $\frac{1}{10}$ to $\frac{1}{4}$ grain, according to the preparation employed The various firms which manufacture organotherapeutic extracts indicate the suitable dose of their preparation In all cases where undue loss of weight is associated with signs of toxæmia and neuromuscular instability, and where no organic lesion can be discovered, the combination of thyroid and parathyroid extract is worthy of a trial

## CHAPTER VII

## THE PITUITARY BODY (HYPOPHYSIS CEREBRI)

### Introduction.

THE structure and development of this gland has been described in Chapter II It was seen to consist of three parts—an anterior or glandular part, a pars intermedia, and a posterior or pars nervosa

In this chapter we will discuss diseases of the pituitary, the signs and symptoms of disorders of its function, and the therapeutics of pituitary extract.

It is perhaps true to say that, with the exception of the thyroparathyroid apparatus, the pituitary has come more into notice of recent years, and our knowledge of its functions and utility as an organo-therapeutic product has increased more than any other of the internal secretory organs It is true that the suprarenal bodies have loomed large, but so far the therapeutic possibilities of their secretion have not developed to the same extent The work of Cushing on this subject has added enormously to our knowledge, both of its functions and disorders.

### Diseases of the Pituitary.

Under this heading we shall discuss both diseases and disorders of the function of the pituitary. The easy route by which to approach this rather difficult

subject is to consider it from the same standpoint as we did the thyroid—namely, its over-action or hyperpituitarism, and its under-action or hypo-pituitarism To continue the study, we have a condition analogous to the thyroid "wobbling"—a condition presenting features which are a blend of the two states of over- and under-action, and which has been termed "dyspituitarism"

### *Acromegaly (Hyperpituitarism)*

This disease was first associated with the pituitary gland by Marie more than twenty years ago

It is characterised by overgrowth of the bones, more particularly those of the face and extremities, disorders of metabolism, shown by polyuria, obesity, and glycosuria, changes in the visual field, headache, amenorrhœa, and general weakness The disease is more common in women than in men, and appears in adolescence or early middle life

The early stages are characterised by pains in the head and extremities, feelings of weakness and languor, and in women amenorrhœa After a variable interval, the changes which have given the name to the disease are seen The facial appearance alters, the nose enlarges the face and jaw are widened transversely, the ears become larger and thickened, while the prominent eyebrows complete the facial change At the same time the fingers alter, becoming "sausage-shaped" the hands broaden, and the nails become flat and ridged The skin of the hands, feet, and face becomes thickened and tough and the tongue enlarges There is often narrowing of the visual field, sometimes double temporal hemianopia, or varying degrees of optic atrophy

The bony changes are no less characteristic; the

wrists are often small, but the hands large, while the feet are also enlarged The spine may be bent into a kyphosis, and there may be some diminution of stature in consequence

The age at which the disease first manifests itself is important in determining the clinical picture If it ensues during adolescence, the condition of gigantism may result; whereas if the disordered function does not appear until adult life, the changes described above, but not associated with enormous stature, will be seen

Associated with these signs, the changes which have been noted in the endocrine organs are of interest The thyroid gland is "sometimes hypertrophied, sometimes atrophied", the thymus has been found to be persistent, and the pituitary body has been found, both post mortem and after operation, to be the seat of changes, sometimes of a marked nature The sella turcica shows enlargement to the X rays, and tumours of the pituitary body have frequently been found in association with the symptoms of acromegaly

While originally, therefore, it was thought that acromegaly was due purely to hyperpituitarism, this opinion can no longer be held Tumours have often been found in acromegalics, and the disease appears to have been arrested by their removal, but other views of the pathology of this disease have now been put forward

The problem of the changes which underlie the acromegalic condition is full of interest It will be seen that the signs and symptoms vary within very wide limits, which is only partly explained by the age of onset It may be said without exaggeration that, in some cases, symptoms suggestive of hyperpitui-

tarism are predominant, while, in others, the more striking features are those of deficiency of the secretion. As we have suggested in the case of the thyroid, this is best explained by the hypothesis that at one stage there is over-secretion, at a subsequent one under-secretion, and that the patient may be seen at a time when any intermediate degree is present. This would account for the apparently wide range of the symptoms.

Let us review some of the abnormalities which have been found in conjunction with acromegaly. The condition of gigantism is seen in some cases, while exophthalmic goitre, glycosuria, adrenal implication and thymus persistence, parenchymatous goitre, are some of the disorders which have been found associated with acromegaly.

While, originally, acromegaly was considered to be due to hypersecretion of the pituitary (just as Graves' disease was attributed to hyperthyroidism), now it is necessary to modify that opinion, in view of many new discoveries. Chief among these must be mentioned the implication of the thyroid, for many cases are now recorded in which the thyroid has been found deranged. Sajous states that in the earlier stage of the disease (the sthenic stage) the thyroid and the adrenals are rendered over-active by the irritated pituitary. The signs of irritation of the thyroid have been numerously recorded—enlargement, exophthalmos tremors, tachycardia, those of hyperadrenia such as hypernephromas furnish,* general bodily overgrowth and premature adolescence are seen in such cases, and a bronzing of the skin.

* *Op. cit.* pp 610–611. Cases are quoted here which illustrate these points more especially the association of hyperpituitarism with precocity.

not unlike that seen in Addison's disease, has been noted in this disorder

The author just quoted lays considerable stress on the interrelation of the pituitary and other of the internal secretory organs, notably the thyroid, thymus, and adrenals He considers that the pituitary furnishes stimuli to the thyroid, and he cites numerous cases in which myxœdema has been associated with pituitary growths as a proof that the thyroid requires pituitary stimuli for its functional activities In the sthenic stage of acromegaly, the influence of the hypophysis on the suprarenals is shown by the overgrowth, in the later stages, or the asthenic, the exhaustion of the adrenals is widened by the discoloration of the skin, fainting fits and tachycardia, dyspnœa, loss of weight, and progressive debility

### *Hypopituitarism*

The signs and symptoms of deficiency of the pituitary secretion run on parallel lines to those of hypothyroidism As both these glands contribute to the metabolism—to the building up and breaking down of the cell—their absence will be shown by similar features Perhaps it will be easier if we emphasise the differences first, dealing with the common signs later on

The chief difference between the lesser degrees of thyroid and pituitary deficiency lies in the epidermal structures As we have already seen, hypothyroidism is characterised by a rough skin, carious teeth, scanty and "lifeless" hair, and ridged and grooved nails. The skin in hypopituitarism has not these characteristics, it is, on the contrary, smooth and soft The hirsutes is usually abundant on the head, but its

distribution on the body is characteristic. The pubic hair in men is localised, and does not spread towards the umbilicus, as is the case in the healthy male, there is a paucity of the cutaneous hair all over the body, and the combination of smooth skin, rounded obese extremities, usually markedly hairless, is typical.

The subjects of hypopituitarism are usually short, thick-set, with stolid expressions and slow mentality. The degree to which these features are seen in these patients depends upon the period of life at which the deficiency is active. If it commenced during adolescence these features will be seen and the patient can be diagnosed as a hypopituitarism with some degree of certainty.

The signs for which the physician looks in these cases are strikingly like those seen in hypothyroidism, with the exceptions already referred to. The pulse is slow, the temperature subnormal, obesity is marked, and the intellectual powers clouded. These patients, like the submyxoedematous subjects, feel the cold, and usually prefer the summer to the winter.

The disorder first described by Frohlich and named by Bartels "*dystrophia adiposogenitalis*," is an example of hypopituitarism which may be associated with deficient thyroid activity. Cushing believes that the obesity owes its origin to a posterior lobe deficiency in the pituitary, the high sugar tolerance and increased carbohydrate assimilation being due to the same cause.

The symptoms of hypopituitarism may be expected to differ widely according to whether the disease commences during adolescence or adult life. Again, there is reason to believe that the symptoms will be different according to whether the anterior lobe or

posterior lobe be affected. A lesion in the anterior lobe will show its effects mainly upon the stature, while one in the posterior lobe will be associated with undue fat formation and deficient sexual development. Data in support of these statements is somewhat hard to find, as the secretion of the pituitary has not been localised to any different part.

The facts concerning the pituitary are described very fully in Cushing's book, and the reader anxious to learn the latest physiological facts is referred to this work.

Once adolescence is passed, the clinical picture of hypopituitarism will differ materially. There is good evidence that injuries to the pituitary, involving deficiency or loss of its secretion, is followed by obesity, hypothermia, and metabolic disturbances, and a case is on record in which a bullet wound of the infundibulum was followed by marked obesity.

## *Dyspituitarism*

This name has been given to the symptoms which are characteristic of pituitary disturbance, but which are typical of neither over- nor under-action, but are a blend of the two.

It appears probable that some patients showing the symptoms of pituitary disturbance have originally suffered from hyperpituitarism, and will eventually develop the signs of hypopituitarism, much as the subject of Graves' disease can develop signs of myxœdema after removal of the thyroid. Moreover, a blend of the signs of the two conditions—such as sluggish mentality, subnormal temperature, obesity, associated with bony overgrowth, changes in the hair and skin—goes to show that conceivably all stages

between acromegaly and Fröhlich's syndrome might be encountered As we shall see when discussing the therapeutics of pituitary extract, many patients not showing the typical picture of hypopituitarism are benefited by the exhibition of pituitary preparations. This may be due to the homostimulative effect of such extracts, but the wide use of pituitary substance in pluriglandular preparations is some evidence of its utility

The stage at which the patient is seen determines the treatment, for pituitary extract may be useful when over-action has led to partial exhaustion, I hardly before

**Therapeutics of Pituitary Preparations.**—We hav already discussed the physiology of the hypophysis here we are concerned with its utility as a therapeuti agent

It will, however, be best to commence by summarising the effect produced by pituitary extract

1 It raises the blood-pressure, and augments the power of the heart-beat with slowing of the pulse

2 It stimulates the kidney and is therefore a liuretic

3 It causes contraction of involuntary muscle all ver the body, hence it increases peristalsis and is an ecbolic

4 It is a galactagogue

**Emergency Use.**—Pituitary extract has come into universal use to counteract shock and to raise the blood-pressure in collapse It has also been somewhat widely utilised to stimulate the uterine contractions in childbirth

In the first case little need be said, either of its *modus operandi* or its record Its use in this con-

nection is universal It is customary to inject, intramuscularly by preference, about 15 minims of the extract of the posterior lobe. In cases of great emergency it may be given intravenously, well diluted with normal saline A second dose given shortly afterwards does not produce anything like so great an effect as the first

Pituitary extract has been spoken of as the ideal uterine stimulant and hæmostatic Its use in labour depends *upon its power to stimulate the uterine* contractions, and to do so in a manner which is akin to normal labour. This action is interesting in *showing the interaction of the hypophysis and the* genital organs, an interaction to which reference has already been made It is still more interesting when we realise that during pregnancy large granular cells make their appearance in the pituitary (the so-called " pregnancy " cells), possibly to prepare for the time when their influence upon the uterus will be needed

We need not describe the uses of this extract in labour, as these are well known and will be found in many larger books It is given in the second stage to promote contraction, and after delivery to check hæmorrhage

**The Extended Use.**—From the action of pituitary extract, it will readily be seen that its utility is undoubted in a wide *variety of derangements* We will deal first of all with its use in diabetes insipidus

This condition is believed to be due to a disease or lesion of the pituitary body, probably the posterior lobe It is characterised, as is well known, by the passage of large quantities of urine, but not containing sugar—such as occurs in true diabetes Recently the evidence of the power of injections of pituitary to control the polyuria—at all events temporarily—has

been accumulating, and Davidson has reported a case under the heading, "The Antidiuretic Effect of Pituitary Extract in Diabetes Insipidus," in which injections of pituitary caused a marked fall in the amount of urine passed daily By the mouth, however, no such effect was produced There is no evidence, however, that this method will cure this disorder

In constipation, and more especially in the intestinal paresis which sometimes ensues after operation, pituitary extract is helpful In the former condition, it is usually administered *per oram*, in the latter, by intramuscular hypodermic injection Injections can be utilised if the extract by the mouth has no effect This extract has also been employed to stimulate lactation, which it does by emptying the lacteal vessels

It is sometimes difficult to obtain results with pituitary preparations by mouth, and recourse to hypodermic medication is then indicated Goetsch has stated that the subcutaneous injection of the extract in dogs was more effective, in the ratio of 4 to 1, than oral administration while the intravenous was even more effective than the subcutaneous, in the ratio of 2 to 1 For prolonged administration, however, the oral route is the most suitable, and this is particularly true in utilising the extract for hypopituitarism

Examples of this state are seen in those cases of low mental and physical development which are called "backward children" While such patients are by no means always small in stature—indeed, they may be overgrown, they are backward in their lessons and sometimes in the development of their physical functions Pituitary extract frequently helps these children, and Magnier ha ... ed two

cases in which extracts of the anterior lobe materially assisted towards the normal rate of development.

With regard to the use of this extract in cases of hypopituitarism, the indications are not always clear, and frequently may be called sketchy. As we saw in Chapter III, an extract may be utilised to replace a deficiency in an effort to restore the hormone-balance, or for its physiological properties. Pituitrin or a similar extract may be used for its physiological properties, more frequently the prolonged use of pituitary extract is similar to the use of thyroid in sub-myxœdema—namely, because a deficiency is assumed to be present, the symptoms of which the physician is attempting to banish by his treatment. Thus, the subject of chilblains, the obese or sluggish individual, the sufferers from constipation, undue fatigue, neurasthenia, and the like, are sometimes remarkably amenable to the exhibition of this extract.

Like thyroid extract, a field of utility has been claimed for pituitary in the treatment of some skin affections. Scleroderma is among these, and benefit has been reported by its use. It is not quite easy to see why pituitary should have been more efficacious than thyroid in such a disorder, it may be by its stimulating effect upon the thyroid and adrenals that it exerts its action.

The rationale for the administration of pituitary extract in patients showing signs of retarded development rests chiefly upon experimental evidence. Removal of the posterior lobe is not followed by symptoms of anything like the severity which ensues when the whole gland, or alternatively the pars anterior, is removed. In this latter case the animal ceases to grow, becomes fat and mentally dull. Symptoms analogous to these in growing children

call for the administration of pituitary extract; but when given by the mouth the effects are believed to be due to the anterior part, as the posterior part can only be absorbed from the stomach, being destroyed in the intestine by trypsin. Moreover, the removal or destruction of the posterior lobe is not, experimentally, followed by the symptoms which ensue after removal of the anterior lobe

Pituitary extract has been used in the treatment of amenorrhœa, and with some degree of success It is possible that more extended trial will prove this application to be really useful, particularly in adolescents who fail to establish the catamenia, and suffer from retarded metabolism associated therewith Williams reports a case in which amenorrhœa was controlled by doses of 10 grains of pituitary extract three times a day In this case other treatment had not proved efficacious

Among the miscellaneous uses of pituitary extract, we may refer to its use in rickets, osteomalacia, and hypothyroidism, in the latter condition it may perhaps be regarded as a useful adjuvant to general treatment It has been given in rheumatoid arthritis, and one observer at least speaks in high terms of his results When we consider that this disease is essentially associated with metabolic disturbances, it is probable that this form of opotherapy will help *in its treatment*

The preparations and dosage will be found in Chapter XII

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## CHAPTER VIII

## THE SUPRARENAL SYSTEM

THE importance which is now attached to the endocrine system commenced with the discoveries of the functions of the thyroid gland. More recently the chromaffin system, of which the adrenals are the keystone, has been receiving more and more attention, and has already outpaced the thyroid in many ways. As research has turned its attention to the functions of this system, facts have come to light which illuminate hitherto unexplained phenomena, and explain many details of pathology which had previously been without an explanation

Sajous and other writers lay great stress on the part which the adrenals play in general bodily metabolism, more especially upon their action and interaction with others of the endocrine system

The existence of these small bodies has been known since the sixteenth century, but their importance has only been recognised comparatively recently In 1849 Addison discovered that they were involved in the syndrome which now bears his name, and the symptoms of this disease were attributed to disease of the suprarenal glands In 1894 Oliver and Schäfer made the discovery that extracts of the glands possessed a marked blood-pressure-raising property. In 1900 the active principle of the adrenal glands was isolated by Takamine, and has been termed "adrenalin"

The suprarenal or the chromaffin system consists of the adrenal bodies, and "accessory adrenals" met with in various localities The adrenal glands consist of two flattened bodies—more or less globular in shape, yellowish in colour—situated behind the peritoneum in front of the upper part of each kidney In section they are seen to consist of two portions—the medulla and the cortex. The former is composed of a tissue which stains deeply with the chromate salts (hence the name "chromaffin tissue"), is well supplied with nerves and bloodvessels and has very close relations with the nervous system, which morphologically would be expected. The cortex is composed of columns of cells containing lipoid granules, a doubly refractive lipoid being characteristic of this part of the gland The cortex is much larger than the medulla, and constitutes about 90 per cent of the gland

In man and the higher mammals this paired arrangement of the adrenals is found, but in lower mammals the medulla and cortex are found intermingled, and are called the "interrenals" Examples of interrenal or adrenal tissue in other parts of the body are the carotid gland, the intercarotid body, accessory adrenals, and adrenal "rests"—such as are stated to occur in the testis While the medulla of the suprarenal gland has close connection with the nervous system, and whilst its secretion has similar actions to that of the sympathetic nerve-endings, the cortex has the same sympathetic connections It is believed that it is concerned with neutralising toxins, and that its secretion has a myotonic action, as opposed to the angiotonic action of the medulla

The relation of the adrenals to the development of the sexual characters is not without interest. Over-

action or tumours of the adrenal cortex have been found in association with sexual precocity, or even with the production of characteristics of the opposite sex; this is substantiated by the belief that accessory adrenal tissue is located in the interstitial gland of the male and the corpus luteum of the female.

The cortex then, briefly, is concerned with sex-characters and muscular energy, the medulla being the seat of the angiotonic hormone

## Adrenalin.

The active principle isolated from the suprarenal gland, and termed "adrenalin," has been prepared synthetically, its chemical formula being ortho-dioxy-phenyl-ethanol-methylamine It possesses certain definite physiological characteristics, and is apparently necessary for the continuance of life, as removal of both adrenals is fatal

The most characteristic feature of this substance is its power to raise blood-pressure, even when small doses are injected The main action is upon the musculature of the vessels, producing constriction of the arteries and capillaries, due to excitation of peripheral nerve-endings, and stimulation of the cardiac musculature This is shown, as pointed out by Biedl, by an increase in both the rapidity and power of the cardiac contractions The action of adrenalin is "wholly confined to tissues with a sympathetic innervation, and, moreover the effect of adrenalin, in any part of the body, is identical with that produced by electric stimulus of the sympathetic nerve supplying that part Where the influence of the nerve is stimulating, exciting contraction or promoting secretion, the action of adrenalin

will also be stimulating Where, however, irritation of the nerve is followed by inhibition, the injection of adrenalin will also produce inhibition "*

Experimentally, one-twentieth of a milligramme, when injected into an animal, is sufficient to cause a considerable rise in the sphygmomanometric reading, which result is even more noticeable if the vagus is put out of order This effect is produced by a vaso-constricting action upon the walls of the peripheral bloodvessels, adrenalin reduces the volume of blood in the viscera, and increases that in the extremities

Adrenalin, therefore, may be regarded as a hormone, necessary to the maintenance of the vaso-motor tone of the body Its effect upon blood-pressure and cardiac response is well established, and in conditions of hypoadrenia, the diminution of the adrenal secretion is shown mainly by lowering of the vascular tone, accompanied by lack of muscular energy

## DISORDERS OF THE ADRENAL SECRETION.

In this section we shall discuss the better-known disorders of the suprarenal secretion, and refer briefly to less well-established syndromes where adrenal disturbance is believed to be concerned

### Hypoadrenia or Adrenal Insufficiency.

The varieties of this are differently described by various authors, but, in the main the conclusions reached have much in common To take the divisions adopted by Sargent, we find three main groups—the chronic, the subacute, and the acute The best

* Biedl, "The Internal Secretory Organs," p. 189

known example of chronic hypoadremia is that furnished by Addison's disease In this disease there is progressive muscular weakness, a low blood-pressure, coldness of the extremities, and a pigmentation which is characteristic of the condition Gastro-intestinal disturbance is frequent, with vomiting and diarrhœa; attacks of syncope or actual heart-failure occur in the later stages of the disease. Associated with these symptoms, there may be found an enlarged spleen, a persistent thymus, hypertrophy of the lymphoid tissue of the body, particularly that of the stomach and intestines

This constitutes the clinical picture of a serious hypoadremia, and, as Elliott has pointed out, all the symptoms except the pigmentation can be explained by the vaso-motor derangement and the paralysis of the sympathetic nerves This, again, emphasises the close relation existing between the chromaffin system and the sympathetic nerves Possibly the pigmentation may be due to involvement of others of the endocrine system by the adrenal insufficiency

Milder degrees of hypoadremia can be recognised by symptoms of vaso-motor instability and muscular weakness and asthenia; indeed, many cases labelled "neurasthenia" are instances of adrenal deficiency. *It is believed that the convalescence* which follows acute illnesses may owe its features to an adrenal deficiency, it suggests that some, at least, of the symptoms of the disease itself may be due to this cause

*In brief, the signs of hypoadremia* may be stated thus a low blood-pressure, a subnormal temperature, a headache of a "vacuum" nature, and the *dermographic sign* which Sargent has described This consists in a white line which appears on the skin of

it is well worthy of a trial; and one or two cases are on record which encourage this view.

Adrenalin is unreliable when administered by the mouth, and better results have been claimed by the exhibition of dried adrenal substance in one of the many forms obtainable, or even by its inclusion in a fluid form, such as an elixir.

From the therapeutic standpoint its utility can be divided roughly into two classes—its local or surgical uses, and its more prolonged or medical uses

## Surgical Utility.

Adrenalin has a wide range of utility in producing local anæmia, and is used in conjunction with novocain or some similar local anæsthetic. In many operations where bleeding is undesirable, such as in nasal, buccal, urethral or rectal procedures, adrenalin is of great help It is not, of course, desirable to utilise large doses, as untoward results have been recorded These take the form of gastric disturbance, anginal pains, giddiness, and fainting I have seen symptoms such as these follow even small doses of the gland given by the mouth, and this convinces me that it is (at least, sometimes) absorbed from the alimentary canal Hypodermic doses, therefore, should be small, about 10 to 15 minims of 1 in 1,000 solution being somewhere about a suitable dose This produces local anæmia, as shown by a blanching of the part

[illegible] can be absorbed by mucous membranes, [illegible] they are abrased, and toxic results have [illegible] pecially from its employment in the

[illegible] is administered to combat surgical

internal secretion of the chromaffin tissue His views emphasise enormously the part played by this secretion, at the expense of certain of the other ductless glands (i e, the pituitary), and he maintains that the pituitary body possesses a centre in its posterior part which governs the activity of the thyroid He believes, therefore, that the adrenals, thyroid, parathyroids, and pituitary, are "*functionally united*" *and form* the adrenal system

We shall see in the next section how these views can be applied from the therapeutic standpoint

## ADRENAL THERAPY.

Extracts of the adrenals have been given in a wide variety of disorders, most of which are associated with muscular weakness, asthenia, or vaso-motor instability From what has already been said, it will be understood that a hypoadrenia is believed to be present in some infections, after acute illnesses, and in such disorders as neurasthenia, myasthenia, and in some neuroses and psychoses

It has been stated that adrenal extracts can cause an ephemeral rise of blood-pressure, but are of little use for repeated or prolonged administration This view has been sustained by the failure of this extract to cure or even improve the health of patients suffering from Addison's disease There is little doubt that it cannot be relied upon to ameliorate the lot of these patients, but, as I have pointed out elsewhere, this may be due to the fact that so large a part of the suprarenals have been destroyed by the disease, it is useless to try and relieve the symptoms by the administration of an extract However, most authorities agree that in any case of Addison's disease

**Toxæmia.**—If, as is believed, one of the functions of the adrenal system is to defend the organism against poisoning from any source, we shall expect to find some degree of adrenal exhaustion in all long-standing toxæmic conditions This is strictly parallel to the submyxœdema which follows upon over-activity, and whether the thyroid is simply a part of the adrenal system, as Sajous maintains, or is an independent entity, as is usually believed, the result from this standpoint will be the same—namely, an exhaustion of the gland or glands The administration of adrenal extract, therefore, is indicated in such conditions, either by itself or in conjunction with thyroid extract It is possible that the improvement in the nutrition which has been reported in cases of cancer may be due to the power of this substance to neutralise toxæmia The belief that toxæmia is associated with adrenal exhaustion is founded upon the fact that, in individuals who have succumbed to an infection, there has been found a "marked diminution of adrenalin"

**In Acute Infections.**—It follows upon this, that adrenal therapy will have a field of usefulness in such ailments as the exanthemata, in septicæmia, and in the exhaustion states consequent upon them; and that its utility may be increased by administration before the collapse is an established fact From what is known of the pathological changes seen in the fevers, from the nutritional changes and the clinical features in general, it will readily be admitted that a first line of attack upon the invading organism is required If we cannot produce a specific to attack the invader, the next best plan is to anticipate the ravages he is likely to commit and prevent them

This, perhaps, will be possible in the future by

shock or collapse, it should be given well diluted with normal saline. Crile has shown that such administration is capable of countering shock and even of sustaining life, combined with artificial respiration, he succeeded in keeping a decapitated dog alive over four hours It can be employed, clinically, to combat any condition of shock, associated, as such a state always is, with a fall of the bodily temperature. Five minims of adrenalin to a pint of warm saline can be given intravenously, and repeated in due course if required

This extract has also been utilised in hæmorrhage from the mouth—*e g*, tooth socket, pharynx, œsophagus, and gastro-intestinal tract Small doses should always be given for the last-named condition, as, owing to its power of raising blood-pressure when absorbed, large doses will cause a preliminary increase in the bleeding The dose may be determined by commencing with a dose of 0 001 milligramme (Sajous), and increasing this gradually, a careful watch being kept upon the blood-pressure

Adrenalin has also been utilised in the treatment of cancer, and it has been stated that injections around a carcinomatous growth of the tongue proved beneficial, that, administered by the mouth, it has delayed the cachexia, and even caused an increase in the bodily weight

## Medical Utility.

The clinical states already referred to as hypoadrenia offer the widest field of utility for this treatment The signs and symptoms of these have already been described We can here draw attention to some concrete examples of adrenal insufficiency.

Its use has been advocated in phthisis, more especially those cases where asthenia and hypopiesis are a marked feature, and where the loss of strength appears out of proportion to the severity of the disease. It is, of course, necessary to bear in mind the effects which this treatment will produce upon the vascular tension and the liability to hæmoptysis

In hay fever adrenalin has gained some reputation as a nasal spray, but it appears that its use should be for a short time, or as an occasional application only, otherwise congestion is apt to follow upon constriction.

organotherapy; even now many clinicians are finding adrenal therapy to be of great help in conditions leading to exhaustion As an example of this, Sargent has laid emphasis on the association of hypoadrenia with typhoid fever. This observer believes that exhaustion, lowering of the temperature and blood-pressure are a sign of the failure of the adrenals, and that when this ensues upon the features which constitute the earlier stages of most fevers (including typhoid)—excitement, restlessness, pyrexia, etc—we have reached the stage of adrenal insufficiency It appears, moreover, that the symptoms of adrenal insufficiency rapidly disappear when adrenal extracts are administered Another disease, believed to be associated with adrenal under-activity and to be amenable to this form of therapy, is "Asiatic cholera," one observer stating his belief that the cholera syndrome is an acute hypoadrenia

**Cardiac Disorders.**—We have already referred to the employment of adrenal extract in cardiac failure, but it can be utilised as a cardiac tonic in cases which are not acute Many observers have noted the beneficial results which have followed the administration of this extract, as it is, of course, a direct cardiac excitant, and according to Sajous an indirect excitant also, viâ the coronary arteries

***Pulmonary Disorders.***—*Adrenalin has been injected* to relieve an attack of asthma, and its utility is undoubted in this direction. Ten drops of the 1 in 1,000 solution injected hypodermically is followed by almost immediate relief The administration of the extract in daily doses for bronchitis has much to recommend it, and for individuals liable to bronchial disturbances associated with spasm adrenal therapy is well worth a trial

of dilute hydrochloric acid into the alimentary canal is followed by a marked increase in the pancreatic secretion, which is brought about by the acid coming into contact with the walls of the duodenum This produces a hormone possessing the property of stimulating pancreatic secretion. The entrance into the alkaline duodenum of the acid chyme releases this substance, secretin, from its precursor prosecretin This secretion has been called the principal alimentary hormone, and it is present in all animals An analogous substance—gastrin—is present in the stomach, which acts upon the oxyntic and peptic glands of this viscus, with the object of stimulating them into activity

Secretin, moreover, acts upon the walls of the ileum, assisting the production of the succus entericus, it stimulates the production of bile, and it is said that the stools typical of jaundice have been rendered normal in colour by a few doses of secretin This substance, therefore, may be regarded as an excitant of the motor functions of the bowel, both by virtue of its action upon the intestinal juices and by reason of its stimulating action on the biliary secretion. But it is necessary for some other chemical to be present, as is the case with blood, for Huston has shown that secretin alone is incapable of stimulating the pancreatic juice in the absence of blood Much of the good which follows the prescription of acid mixtures in ' indigestion " may be due, as suggested by Harrower, to the release by the acid of the internal secretin of the stomach and bowel

Little is known of the actual constitution of secretin It is not a ferment, but like other hormones it is a substance of low molecular weight, it is not formed until it meets enterokinaise, which,

## CHAPTER IX

## THE INTERNAL SECRETIONS OF DIGESTION

### The Salivary Glands.

THERE is some evidence to support the view held by some that there is a salivary hormone which is a part of the endocrinous system Facts of clinical interest show that there is a close connection between the parotids and the testis and ovary—as witnessed by the metastatic involvement of the latter glands in "mumps" Certain observers also have tried administration of extracts of the parotid to prevent ovarian pain and enlargement, and some have reported beneficial results from this treatment.

A relationship has been suggested between the salivary glands and others of the digestive glands, notably the pancreas, one author reporting three cases of parotitis which led, he believes, to acute pancreatitis Presumably, the association here is by a humoral channel

The clinical experience and literature upon this subject is scanty, although it is highly probable that the metastatic changes so well recognised as occurring in mumps do occur in other glands, such as the pancreas If further experience supports this hypothesis, there may be a wide field open for organotherapy

### The Gastric and Intestinal Secretions.

In studying the work of digestion, we encounter examples of true hormonic action The introduction

of dilute hydrochloric acid into the alimentary canal is followed by a marked increase in the pancreatic secretion, which is brought about by the acid coming into contact with the walls of the duodenum This produces a hormone possessing the property of stimulating pancreatic secretion. The entrance into the alkaline duodenum of the acid chyme releases this substance, secretin, from its precursor prosecretin This secretion has been called the principal alimentary hormone, and it is present in all animals An analogous substance—gastrin—is present in the stomach, which acts upon the oxyntic and peptic glands of this viscus, with the object of stimulating them into activity

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again, is not formed until the acid chyme enters bowel This latter ferment mainly reinforces try activity, but also influences the fat-splitting ferm of the pancreas The formation of the secre known as succus entericus is also a matter of so doubt; it is believed that two conditions are necess for its formation—namely, the presence of the p creatic juice and the distension of the bowel contains the ferment to which we have alrea referred, enterokinaise, erepsin, which completes digestion of proteids, and several fat-splitt ferments

## The Liver.

Apart from the production of bile, into the deta of which we need not enter here, the liver perfor many other important functions In brief, the liv is responsible for the production of bile, with the bi salts, pigments, and ferments, it is concerned in t regulation of the sugar content of the blood, and the control of nitrogenous metabolism; it regulates th power of coagulation of the blood, is concerned wi the destruction of toxins reaching it from the bowe and in the prevention of such substances fro reaching the cells of the body—i e, it acts as a filt between the gastro-intestinal tract and the genera blood-stream

Apart from this, there is a considerable evidenc that the liver possesses an internal secretion analogou in its workings to that of the pancreas, inasmuch a its secreting powers depend upon stimulation by chemical means *Thus, the production of bile i* increased by secretin, and, if this secretion of the live is stimulated by a hormone, it is more than probabl that others emanating from this gland are also so activated

### The Pancreas.

This, most important of the digestive glands from the internal secretory standpoint, deserves a little closer study. It is a tubulo-racemose gland, situated transversely across the posterior wall of the abdomen In structure it resembles the salivary glands, although it is of softer consistency than these organs It consists of a head, a neck, a body, and a tail, and the duct is known as the "canal of Wirsung" This opens into the duodenum, either in common with the ductus communis choledochus or else by an independent orifice Among the alveoli, loosely held together by connective tissue, are the cells known as the "islets of Langerhans" From the endocrinological standpoint, these cells are of prime importance, for they secrete a hormone absolutely necessary to the bodily metabolism The digestive juices of the pancreas are stimulated by the substance to which we have already referred under the name of "secretin"

In 1889 von Mering and Minkowski made the important discovery that removal of the whole or a large part of the pancreas was followed by hyperglycæmia, and eventually fatal diabetes This is not due to the removal of the external secretion of the pancreas, for if a portion of the gland is grafted into the animal, glycosuria is prevented Again, if the pancreatic duct be tied, the pancreatic tissue atrophies, but it is believed that the islets of Langerhans remain in a sufficiently normal condition to furnish the body with the internal secretion Again, it has been noted that these cells are sometimes degenerated in cases of diabetes, which is strong presumptive evidence that, at all events in some cases, this disease owes its features to interference with the islet substance It

may be assumed, therefore, that the islets of Langerhans secrete a substance which, circulating in the blood-stream, prevents an undue amount of glucose from accumulating in this fluid Hedon has shown, by passing the blood of normal animals through a depancreatised dog, that glycosuria may be prevented. This suggests that normal blood contains some substance or substances which regulate carbohydrate metabolism

With reference to the relation of the pancreas to diabetes, many authorities believe that the islet tissue of the pancreas is essential to normal carbohydrate metabolism, and Von Noorden maintains that no diabetes can exist without disease of the islets of Langerhans This author divides interference with the islet tissue into two groups, the first resulting from diseases of their environment, the second from specific disease of the islands themselves Other authors lay stress upon diseases of a bacterial origin attacking the islet substance from the duodenum and thus setting up a pancreatitis When the pancreatitis is relieved the pressure disappears and likewise the glycosuria

The pancreas possesses a close relation with others of the endocrine system This is shown by such variations from health as hypothyroidism, with its tendency to increased sugar storage, in hypopituitarism there is a similar metabolic change, while in hypoparathyroidism there is the opposite condition present The thyroid and pituitary, therefore, influence carbohydrate metabolism in the opposite direction to which the parathyroids do, while the gonads, adrenals, and possibly the salivary glands, have a balancing action upon the pancreatic secretion Injections of adrenalin tend to produce glycosuria;

removal of the internal secretion of the testis or ovary increases the tendency to sugar storage. Obviously, therefore, the secretion of the chromaffin tissue balances the pancreatic internal secretion; while that of the gonads stimulates the storage of carbohydrates

## The Spleen.

This organ, like the liver, is larger than it should be, unless we can attribute to it some function which our forefathers were unable to Just as the liver was regarded with awe on account of its size, which seemed out of proportion to its function as a provider of bile, so the spleen was thought to be unduly cumbersome if its function was that of regulating the supply of white corpuscles The spleen is believed to be "a filter to remove particles from the blood and also the debris of red and white cells It is the seat of formation of lymphocytes and in a lesser degree large mononuclear leucocytes During intra uterine life it has a part in the formation of red cells, but there is no evidence that this continues after birth" (Hutchison)

The question of whether the spleen furnishes an internal secretion has never been adequately settled And for several reasons First of all, the spleen is not a "gland" in the sense that secreting organs are "glands" Secondly, the results of splenectomy show that there is little permanent change in the individual after this operation At first there is a lymphocytosis and a decrease in the number of red corpuscles, but in a few weeks the blood becomes normal It may be, however, that this result is brought about by other structures—*e g*, the lymph glands—taking on the work of the spleen. Thirdly,

no experiments have so far conclusively shown that the spleen elaborates an internal secretion, and no hormone has been elaborated from its substance On the other hand, there are several suggestive points worthy of mention. There appears to be, according to one writer, a relation between pancreatic digestion and the splenic activity; for, according to this view, after splenectomy this part of digestion is almost entirely carried out by the stomach and intestines There is also said to be an increased need for food in splenectomised animals, in whom digestion is not so perfect

These statements are not very satisfactory, as they do not establish anything more than a supposition that the spleen is in some way related to the work of digestion Some experiments of Herzen support this belief, and go to show that the spleen secretes a hormone which acts as an activator to the pancreatic secretion

The therapeutic results of splenic extract are undoubtedly good in practice, and can best be explained by the hypothesis that the spleen helps digestion, and that, when removed, the work of digestion either suffers, or that the loss of the splenic secretion is compensated by the work of some other organ

Splenic extract is stated by one writer to assist in restoring the functional activity of this organ after it has been impaired by such diseases as typhoid. It increases the leucocytes, and therefore helps in restoring the patient to normal health This author utilised 5-grain doses of splenic extract It has also been prescribed in malaria, and in diseases of the spleen and blood, several authors claiming that both red and white cells are increased by the subcutaneous injection of splenic extract. Thus, a joint communication records the results of treatment by these

means on the blood-count. Injections of 0 2 grain of fresh spleen extract raised the count of red cells from 2,988,000 to 6,816,000, and the white cells from 9,400 to 12,800 Another author states that the injection of 5 c c of splenic extract in tuberculosis will add about two million red cells to the count A second injection after twenty-four hours will "bring the figure to almost six million."

Treatment by splenic extract has been widely used in anæmia, tuberculosis, enlargements of the spleen, enteric fever, leucopenia, and to raise the resistance in infections other than tuberculosis Splenic extract is well tolerated, and is not, for practical purposes, toxic

The clinical results of this extract upon nutrition may perhaps be best explained by the hypothesis already referred to, that it supplies a substance which increases the digestive activity of the pancreas This was advanced by Schiff, and supported by numerous other authors, such as Herzen and Lepine Laboratory experiments support this theory, for it has been shown that a mixture of pancreas and spleen-pulp possesses more active properties than the pancreas alone

It is not unlikely, therefore that this form of organotherapy will come to be more widely used in the future than in the past For, if it is able to assist the individual in the difficulties of assimilation and absorption caused by a febrile process, such as occurs in tuberculosis, it is going to help in a most difficult problem The present writer has used splenic extract in disorders of nutrition with some success, and a more extended trial will show whether its utility can be relied upon If so, from the digestive standpoint alone, it will probably supersede many accessory digestive agents, and will, perhaps be added to the stock weapons with which we fight anæmia and sepsis.

## CHAPTER X

## THE SEXUAL ORGANS

The importance of the organs of sex in any study of the internal secretions is great Their part in promoting the bodily health, in maintaining adequate metabolism and promoting excretion, and in the production of secondary sexual characteristics, is undoubted. Their interdependence with other of the ductless glands, their "dovetailing" into the work of the thyroid, pituitary, adrenals, and thymus, has already been discussed in a previous chapter.

Here it is proposed to deal briefly with the individual secretions, and to discuss in general terms their therapeutic properties The suitable dosage will be discussed in Chapter XII

### The Testes.

Reference has already been made in Chapter II to the physiology of the testis The organotherapeutic aspect of testicular extract commenced with the pioneer work of Brown-Séquard, who published the results of his experiments upon himself in 1889 Subsequent workers have not confirmed the results he claimed, although a certain measure of success has attended the prescription of orchitic extract in one form or another.

Brown-Séquard claimed that this extract increased muscular power, abolished tendency to fatigue, and rejuvenated the patient in a remarkable degree. He

thought, therefore, that he had hit upon the key which would unlock the door to protracted youth; and that old age corresponded with the cessation of an internal secretion of the testis.

While this may be so, it is equally certain that we are not at present enabled to keep off senility, or to remedy its shortcomings by injecting orchitic extract. Nevertheless, it has its therapeutic uses, and can be made a useful member of the organic pharmacopœia, if its limitations in the direction just referred to are remembered. It is necessary also to bear in mind the results which follow loss of the testes—such, for example, as are seen in capons and in eunuchs—to appreciate the syndrome which is likely to benefit from this method of treatment.

The testicular secretion obviously produces the secondary sexual characteristics, and plays a part in regulating metabolism. Loss of the testes is followed by undue fat formation, overgrowth of the bones of the body, and absence of sexual power. Testicular extract is believed to increase the dynamogenic power of the organism, so that the energy at the disposal of the body is increased. Brown-Séquard himself noted the increased energy at his disposal after injections of orchitic extract, and the fact that he could do more with less fatigue after such an injection. He also noted improved control of the bladder and a better clearance of the bowel.

The uses of orchitic extract are wide, but somewhat difficult to describe. Clinical experience with this extract has convinced the present writer that it is a useful stimulant to metabolism and may well replace inorganic drugs in the treatment of neurasthenic fatigue and kindred disturbances of the nervous system. Indeed, the tired, jaded, poorly nourished

they assist in the preparation of the uterine mucosa for the deciduum

The interstitial gland has had attributed to it functions similar to those ascribed to the corpora lutea It undergoes enlargement during menstruation, and is at its height of development during pregnancy. The parallel between these cells and those found in the testis is, however, not a close one in other respects

The Graafian follicles, which give rise to the corpora lutea, also undergo changes when pregnancy occurs There is proliferation of the epithelium, increase in the size of the cells and the formation of the corpora lutea Many observers believe that these latter bodies give rise to the internal secretions of the ovary, and influences of a widespread character are attributed to this element. Apart from the control of the uterine mucosa during reproductive life, it is stated that the luteal secretion prepares the way for the embedding of the ovum It is believed, and clinical reports certainly support this belief, that the luteal hormone controls the uterine engorgement which precedes menstruation It inhibits ovulation, and sensitises the uterine mucosa for the formation of the maternal placenta (Harrower, quoting Frank) The same author states that there are two ovarian hormones—one produced by the interstitial gland, whose function is to regulate menstruation and contribute to the control of nutrition, the other, proceeding from the corpus luteum, is antagonistic to the interstitial secretion, "inhibiting ovulation during pregnancy" This latter statement (Harrower adds) is questioned, since ovulation has been known to occur during pregnancy In any case, the exact site of the formation of the ovarian secretion (or secretions) is

still unsettled, and we pass in review the functions which are controlled, or partly controlled, by this organ

Undoubtedly the functions of the uterus are controlled by the ovary, and the evidence we have already given makes it unnecessary further to refer to this The relation between the mammary gland and the ovary is a close one, the development of the two organs coincides, and destruction of the ovaries causes arrest in the development of the mammary gland The ovarian influence upon metabolism can be realised by the following facts experimentally, metabolic activities, lowered by castration, are increased by the administration of ovarian extract Again, many instances of the successful control of obesity in women by ovarian extract have been reported, and it has been suggested that hypo-oöphorism may upset the pituitary gland and produce a dyspituitarism Finally, the relation of the ovarian secretion to calcium metabolism has been strongly emphasised by Blair Bell He found that oöphorectomy diminished the calcium salts in the urine by one-half, and he believes that "the ovaries have an active part in promoting the excretion of calcium" The removal of the ovaries has been practised with benefit in osteomalacia, which, again, is suggestive that absence of the ovarian influence produces retention of lime-salts

With regard to the therapeutic aspect of the ovaries, this, as might be expected, is mainly applicable to disorders of the menstrual functions In scanty or irregular menstruation, ovarian extract (or lutein extract) has been widely utilised, and has given good results, at the climacteric there is a wide field for the employment of this substance The sudden loss

of the catamenia is, as is well known, often attended by nervous and mental disturbances If these can be controlled until such time as the re-adjustment of the hormone balance has taken place, a great deal of suffering can be avoided. Some authors believe that the action of luteal extracts is only successful in cases *where the uterus and ovaries are still retained*, so that in patients who have undergone such operations as pan-hysterectomy the administration of these extracts would not give relief It is to be remembered that the supply of the ovarian hormone, so far as metabolism is concerned, must be of a fairly continuous nature in health, and that it would be difficult, if not impossible, to supply an adequate substitute by organotherapy

Two extracts are in use, the extract of the corpus luteum, and the extract of the ovarian tissue (whole gland) The indications for the use of both these extracts are suggested in another place, but considerable difference of opinion exists as to the relative efficacy of these two preparations Extract of the whole ovary has been utilised in hypopituitarism and in delayed epiphyseal ossification, while menstrual and climacteric disorders have, perhaps, been more *successfully controlled by extract of the corpus* luteum

## The Mammary Gland.

The interest in the endocrinological aspect of this gland may be said to have commenced with the experiments of Starling and Lane-Claypon These observers showed that the fœtus was the seat of production of a substance which stimulated the function of lactation, further experiments by other observers have confirmed this

It has been shown, however, that the ovaries exert an influence upon mammary hyperplasia and lactation; in fact, experiments have demonstrated that mammary overgrowth can be produced by rupturing an ovarian follicle, even when the uterus is not pregnant. Again, Basch has found a hormone in the placenta, which stimulated lactation and produced hypertrophy of the mammary cells We have, therefore, three possible sources of mammary stimulation

The therapeutics of the mammary gland can be described briefly In 1896 Bell of Glasgow showed that extracts of the mammæ of cows had a galactogogic effect, and since then other observers have confirmed this Apart from this action, mammary extract has been prescribed to neutralise ovarian over-activity, as it is believed that an antagonism exists between the mammary and ovarian hormones Thus, it has been given to check menorrhagia, and to control uterine hæmorrhage and congestion It has been prescribed in the treatment of uterine fibroids, and it is claimed that both the hæmorrhage and pain are relieved Thyroid is sometimes combined with the mammary extract, and this form of treatment has been recommended as better than the single extract

Mammary extract also is utilised in the post-partum stage, both for the control of the uterus and to stimulate the production of the mammary secretion

## The Placental Hormone.

We have already referred to a placental hormone in connection with the question of mammary activity But the subject deserves a little wider discussion, even if it may appear to be scarcely germane to the subject we are considering

The placenta is concerned, apart from its main function in regard to fœtal circulation and nutrition, with certain aspects of the post-partum period. Ott and Scott, and others, have demonstrated the power of placental extract in stimulating lactation. It has been suggested that the placenta is concerned in the production of eclampsia, but whether as a toxic agent or as an organ whose antitoxic power has failed has not been rendered clear. Various other communications have appeared in regard to the placenta, notably one quoted by Harrower, which suggests that extract of placenta has some power in modifying uterine involution

Recently, some investigators have transplanted ovaries into the uterine córnua, and observed that the uterine mucosa in the neighbourhood of the grafts produced tissue analogous to the maternal placenta

From the therapeutic standpoint, however, the placenta has little to interest the student

## CHAPTER XI

## THE THYMUS, LYMPHATIC GLANDS, AND PINEAL BODY

### The Thymus.

We have already described the anatomy and physiology of this organ (in Chapter II, p 29), and discussed its relation to other of the internal secretory organs We may remind the reader, however, that the thymus and the generative glands show a kind of antagonism The former is active before the full development of the sex organs takes place, and it has been shown by experiments and in human beings that delay in the onset of puberty is associated with persistence of the thymus

#### *Thymus Persistence*

It has been generally taught that the thymus persists up to the age of puberty or thereabouts, and then atrophies, leaving a fibrosed remnant in place of the glandular structure of early life The disease known as "status lymphaticus," in which death from syncope is liable to occur, is associated with persistence of the thymus and hypertrophy of other lymphatic tissue throughout the body It is possible that the atrophy of the thymus which normally takes place permits the increased activity of the gonads, it is equally likely, however, that the introduction of the sexual hormones produces the thymic atrophy Experimental removal of the ovaries causes thymus

hypertrophy, even after the usual regression has occurred, and removal of the latter gland is followed by premature development of the organs of sex (Paton)

It has recently been suggested (Dustin) that the thymus atrophy at or about the age of puberty is not as universal as has been supposed This author states that sections through the thymus of individuals who have died suddenly from accidents show this gland to be rich in lymphocytes, and consequently in chromatin Another writer maintains that the thymus is rarely atrophied in young adults who have succumbed rapidly to wounds, and that in many cases such thymic enlargement was associated with small thyroids

### *Relation of the Thymus to the other Endocrine Glands.*

The thyroid has been shown to bear a close relation to the thymus In a large proportion of cases (*76 5 per cent, Mattie*) *of patients who had succumbed* after operations on the thyroid, thymus persistence was noted It is known that many sufferers from exophthalmic goitre have been found post mortem to possess an enlarged thymus Again, it has been suggested that where the goitre is small, and yet symptoms of pressure and dyspnœa are prominent, there may be enlargement of the thymus "It is this symptom which, suddenly aggravated, may end in death, after an operation on the thyroid "*

[illegible] between

[illegible]

in goitre and in Graves' disease Owen was the first

* Sajous, *op cit*, p 224

investigator to utilise thymus in the treatment of the latter disease, and subsequently many observers have reported favourable results from this method Some writers prefer thymus extract to any other organic preparation, most of the reported results are good, and it is quite the exception to encounter a patient in whom the symptoms were aggravated Simple goitre was also treated by Owen with thymus, and Mikulicz reported eleven such cases, ten of which were attended with success

Some interrelation between the thymus and the parathyroids has been suggested, and one author draws attention to *fragilitas ossium*, which he attributes to thymus insufficiency reacting upon the parathyroids

There is little known about this, but a common link may be found in the influence which both these organs exert upon the calcium metabolism of the body

### *Thymus and Calcium Metabolism*

It has been known for years that the thymus is in some way related to the calcium metabolism of the body, and that it influences the ossification of the epiphyses Recent experiments have shown that animals from whom this gland has been removed suffer from softening of the lower bones, and are liable to spontaneous fractures and rickets The condition known as "cachexia thymipriva" has been produced by removal of this gland, and Klose and Vogt* report the result of their experiments in fifty-four dogs After a preliminary increase in weight, great loss of flesh ensued with brittleness of the bones, spontaneous fractures, osteomalacia and rachitis The mental condition changed, the animals becoming idiots These changes pointed most

* See Bibliography

definitely to a disturbance of the calcium metabolism, and showed that there might be a great lack of lime-salts at the disposal of the body It has been suggested that lime-salts, nucleins, and nucleo-proteids are in some way controlled by the thymus, and *that removal of the organ causes* inability to retain these substances, that an acidosis is the cause, both of the calcium deficiency and the idiocy Sajous makes some interesting comments upon the state known as mongolian idiocy, and its relationship to thymus deficiency. Briefly his views are that the function of the thymus is to supply the excess of phosphorus required by the body during growth, and that its failure in this respect leads both to the bony changes and the mental deficiency. *There are many points in common between this state* and cretinism, and Sajous draws attention to these in his work

*A further point in the relationship of the thymus to* metabolism is important, and this also is emphasised by Sajous * The delay in the brain development and the defective growth which follows thymectomy can be remedied by thymus administration or implantation This delay in itself shows the influence which the thymus exerts upon growth and development, *and the non-development of the sexual life* which follows removal of the thymus is further proof that this secretion is vital to the growing organism, this symptom also is counteracted by thymus extract Experimentally, in rabbits, it has been shown that " the thymus attains its greatest weight while spermatogenesis is being prepared, and it is only when the sexual organs are developed that *atrophy of the gland* begins Spermatogenesis continuing, under

* *Op cit* 288–295.

normal conditions, throughout life, we are brought to realise that, as is the case with the bones, the brain and nervous system, the genital system, and, in fact, the body at large, the thymic lymphocytes are specific in the sense that they are abnormally rich in nucleus-building materials. Their rôle is to add to the body during its evolution to puberty, or later, if need be, the excess of nucleins required for this purpose "*

We have already referred to the influence of the parathyroids upon calcium metabolism, and it would appear from the facts just cited that the thymus and [illegible]

loss of calcium from the body; and the present writer, following a suggestion made by Leduc, has noted elsewhere the frequency with which calcium salts are found to be present in the urine in patients suffering from various functional nervous disturbances † This is, of course, an interesting suggestion, that either or both these glands may be deranged in such cases, and parathyroid therapy has certainly helped a proportion of patients whose syndrome resembles that of parathyroidectomy

Hence the hypothesis of one writer that fragilitas ossium is due to both thymus and parathyroid involvement The disease is attributed by this author "to insufficiency of the thymus and the parathyroids, and a beginning hypotonia of the sympathetic system " But against this belief it must be stated that tetany has not been established as occurring after thymectomy, although in this report it was stated to have been latent if not actually present

* *Ibid* , p 288

† " A Manual of Neurasthenia ' pp 269–270, footnote.

*Therapeutic Administration of Thymus Extract.*

Certain disorders in which this extract has been tried have already been referred to Among these we have mentioned simple and exophthalmic goitre, mongolian idiocy, disturbances of the calcium metabolism, and fragilitas ossium Several other disorders will suggest themselves in which thymus extract would be indicated, and conditions arising from, or analogous to, those states produced experimentally by thymectomy are *ex hypothesi* suitable for treatment by thymus extract.

It has been recorded in many instances, notably in the examples quoted from Sajous, that symptoms of cachexia thymipriva occurring after operation can be controlled by thymus extract. It is therefore suggested that states resembling this in human beings should be treated by this extract. Notably, disorders of development, malnutrition, mental delayed development (backwardness), and kindred states, have been known to respond to this treatment In one case, quoted by Harrower, all the routine methods had failed to cause adequate physical development in a boy of sixteen, but 15 grains of thymus extract each day was speedily followed by increasing height and weight and evidences of sexual development.

Other investigators report results from this extract in the treatment of rickets, but from what has already been said it would seem desirable to combine this treatment with the administration of calcium salts, food rich in nucleins, and the digestive and hygienic aids usually employed

Its utility in exophthalmic goitre is supported by a considerable weight of evidence Maude reports a case in which large doses produced considerable im-

provement, the patient relapsing when the treatment was interrupted. Another writer, however, stated that only the nervous symptoms were improved, and this is easily understood when we correlate the excessive loss of calcium in this disease, and the control on this part of metabolism which the thymus has been shown to possess

Thymus extract is not toxic in suitable doses, and as much as 45 grains can be given daily The average dose is from 5 to 15 grains two or three times a day, increased as its effects are noted It is contraindicated in the gouty diathesis, and is not suitable for the individual with high blood-pressure, plethora, or obesity

## The Lymphatic Glands and Miscellaneous Tissue.

While there is no definite proof that the lymphatic glands are hormone-secreting bodies, this has been asserted, and as the extracts of the lymphatic glands are in use therapeutically, a brief reference is indicated We shall also deal in this section with the tonsil, and with extracts of such tissues as the brain and spinal cord, kidney, lung, etc

### *The Lymphatic Glands*

Because the chief function of this system is to protect the body against invasion, it has been suggested that this is brought about by an internal secretory mechanism There is no proof of this; indeed, there is little to support such an hypothesis, although one observer found that tubercle bacilli lose their virulence when placed in contact with emulsions of the lymphatic glands Nevertheless,

extracts of these bodies have come into a limited use, more especially in relation to disorders characterised by lymphatic hypertrophy.

*Lymphatic and Thymus Enlargement*

This syndrome, to which we referred when considering the thymus gland, consists in general lymphoid overgrowth associated with a persistent thymus It has been said that the thymus, during the period of activity, "occupies a dominating position over the lymphatic apparatus," and that, in all probability, the interrelationship between the thyro-lymphatic system and other of the internally secretory organs is a close one The spleen, it is said, "is 'prepared' by the thymus to take up some of the latter organ's still unexplained functions after its involution "*

*Status Lymphaticus.*

This is a condition in which the thymus persists into adult life, and the lymphatic tissue all over the body is hypertrophied The patients are often obese, there is sometimes evidence of rickets, and sudden death, sometimes during the administration of an anæsthetic, often brings the hitherto unsuspected condition to light Such a symptom-complex, if discovered before a fatal issue, which is rarely, if ever, the case, might respond to treatment by means of thymus and lymphatic gland extract, but no data are to hand, and the subject is entirely speculative. Such treatment, moreover, would be theoretically sound only on the grounds that the hypertrophy was the response of the organism to an increased need of the secretion of one or both tissues

* Harrower, p 233.

*Tonsillar Hypertrophy.*

Lymphatic gland extract has been utilised in the treatment of enlargement of the tonsil and growth of adenoid tissue A similar hypothesis underlies this treatment One author states that, in a large number of children with this hypertrophy, a few grains daily of lymphatic gland extract produces a marked improvement in the breathing and a diminution in the size of the tonsils So far as I am aware, this extract has not been tried in any large number of cases, and therefore it is not possible to express an opinion of any value as to its merits.

*In Tuberculosis and Infections*

We referred in another place to the utility of splenic extracts in raising the bodily resistance to tubercular and other infections Extract of the lymphatic glands has been employed for the same purpose There is no evidence, however, that it is of any value, although it is quite possible that it may be shown in the future that some secretion is manufactured by this tissue Until this has been shown or, alternatively, until clinical experience has proved the utility of such prescribing, the method need not detain us further

It may be mentioned, however, that it has been tried in Hodgkin's disease, but at present little is known of its effects One case is reported where benefit accrued from its administration

*The Tonsils*

These bodies are interesting in this connection, if only from the frequency with which they hypertrophy. It has been suggested that their function is

to supply phagocytes to the mouth and throat, and that they, in some way, prevent infection from reaching the blood-stream Another suggestion is that they supply a hormone which influences the circulation and the renal excretions, some experiments recently recorded, where tonsillar extracts were employed, giving some ground for this belief. Extracts of most of the glands, when injected, cause an increase in the volume of the kidney of a temporary nature. There is little proof that tonsillar extract does more than this, although Ott states that tonsillar extract appears to him to be a stronger diuretic than the pituitary, parathyroid, or pineal gland

It is conceivable that tonsillar extract might be utilised in conjunction with lymphatic extract for the treatment of tonsillar hypertrophy, on the assumption that the enlargement is a defence hypertrophy, and not simply the result of infected crypts But this is, of course, purely empirical at present

*Extracts of Nervous Tissue*

For some years extracts made from the brain and spinal cord have been utilised for therapeutic purposes This is, of course, a strictly organotherapeutic procedure, if we believe that healthy tissues contain substances which are of use to the individual The question can be studied from two view-points First, that the brain substance (for example) has chemical properties which can be transferred to the individual who ingests it, and secondly, that brain and nerve tissue has a secretion which it elaborates, and which can be retained in a preparation for prescription In both cases the exhibition of a preparation of nerve tissue would be valuable, in the first instance, because it is rich in lecithin, cholesterin, and lipoids, and is

therefore better than many other articles of diet; in the second, because the hormone (at present unproven) would act as a stimulus to other of the internally secreting organs, the combined work of which results in health.

By such reasoning, however, we come back to the medicine of the ancients—to the Chinese doctors, half magician, half physician, who prescribed gruesome remedies, composed of parts of the body, taken from corpses, or to the period of the "eye of newt and toe of frog" of Shakespeare But such therapy as we are discussing is a little more secure in its foundations than this For extracts of the brain and nerve tissue contain definite chemicals, which, indeed, are the highly phosphorised substances which have gained such repute in the treatment of functional derangements For all we know they may contain a specific secretion as well—that is, specific to the tissue and necessary to the working of that tissue Certain experiments lend some support to this view, it may be, on account of the antitoxic and antispasmodic properties which have been ascribed to these extracts

Combinations of these extracts with such tissue as the lymphatic glands, extracts of the testis, and ovary, have gained some degree of popularity in the treatment of ill-defined neuroses Further reference to the subject will be found under "Pluriglandular Therapy"

### *The Pineal Gland (Epiphysis Cerebri)*

This little gland has been described on p 31, and it was there stated that it appeared to have some interrelation with the sexual secretions Cases have been recorded in which obesity and marked sexual development have been associated with tumours of

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the pineal body. Based upon these observations, and arguing along lines parallel to those concerned in pituitary tumours, some observers have utilised pineal extract in the treatment of backward children, and have claimed improvement from the treatment. De Cyon has studied the pineal gland and its functions, and while he originally held that its function was mainly mechanical, controlling the entry of the cerebro-spinal fluid into the third ventricle, this is now by no means the only function which has been attributed to the gland. It is suggested that it has an inhibitory action upon the sex glands (removal of the pineal has resulted in sexual precocity); that it may be a diuretic and galactagogue, as pineal extracts have this effect when injected, and that it must have some share in the control of metabolism, as tumours of the gland are associated with adiposity. Pineal atrophy is stated to occur after castration, while the pituitary hypertrophies; it is therefore believed that, certainly in some respects, these two glands are antagonistic.

Dana and Berkeley, who have made a study of this body, believe that the pineal gland is concerned with nutrition in early life, including the development of ex, the subcutaneous fat, and growth of mind and ody. There seems to have been undoubted improvement in the mental states of some patients treated by pineal extracts, and it is therefore to be hoped that further light will be thrown on both the physiological and therapeutic aspects of this gland.

## Miscellaneous Organotherapy.

When we come to consider the administration of different structural parts of the body as organotherapeutic preparations, we are dealing with a reasoning we have already referred to. The theory

underlying such therapy is that each organ adds to the blood-stream which passes through it some substance peculiar to itself Biedl says. "All organs which supply substances which are capable of exciting or in any way affecting the functions of other organs may be described as 'hormone-producing'" Again, "Material which is passed into the blood and lymph from any tissue or organ of the body forms its internal secretion, and organs which are not known to possess any other function than that of passing such material into the blood or lymph are internally secreting or endocrine organs" (Schäfer) In the case of some of the substances we shall discuss, we must go a step further than the definition just quoted, for these preparations are made from separate organs having well-recognised functions, but it is believed that they possess a homostimulative property when taken in the form of an extract

*Lung Extract*

The administration of this extract is based upon the reasoning we have outlined, and it has been given in many diseases of the lung, such as chronic bronchitis, emphysema, asthma, pleurisy, and tuberculosis The first and most prominent supporter of pulmonary organotherapy was Brunet, a Frenchman who has made wide researches into this method, and has given much valuable study to the subject. Harrower, to whose work I am indebted for these details, states that the value of this remedy seems to be greater in chronic purulent infections of the respiratory tract, and that several other observers (Arnogan, Cassaet, and Grande) speak well of this ethod *

* Harrower pp 250-251

*Renal Extract*

Brown-Séquard maintained that there was an internal secretion produced by the kidney in addition to its established functions of excretion Other observers have experimented on these lines, and some have claimed that the administration of renal extract has benefited uræmia and other toxic conditions As against this, however, it must be said that an injection of renal substance would contain the adrenal active principle, and it is to be expected that improvement in the symptoms of a condition such as uræmia would ensue

It has been stated by some clinicians that chronic nephritis has been treated with marked success by kidney extracts, others deny that the treatment is of any value whatsoever, or even affirm that it may be harmful

It is, of course, easy to scoff at such therapy as being empirical, without adequate foundation, and unscientific But the earnest student of these subjects cannot dismiss this form of treatment so lightly, for reports of enthusiasts who have tried kidney substance make it certain that further research is worth while Capitan reports a striking result in a case of uræmia, Roque and Lemoine also speak highly of its efficacy, while Vialard has used the extract in chronic nephritis with relief to the symptoms consequent thereon, if not permanent improvement

## CHAPTER XII

### A SUMMARY OF ORGANOTHERAPY

PREPARATIONS manufactured from the organs of animals are now utilised in the treatment of disease. This practice is based upon the belief that all glands without ducts, and some glands possessing ducts, as well as certain other structures of the body, secrete chemical substances which modify the blood in its passage through the organ Practical organotherapy concerns itself with supplying to the individual the chemicals which are believed to be absent, and the signs and symptoms upon which a particular extract is prescribed have been discussed in the preceding chapters

We may remind the reader of the four classes into which hormone-therapy falls

1 Substitution therapy, where a hormone is supplied to balance a loss

2 Supplementary therapy, where augmentation of a hormone is desired

3 Specific therapy, where the hormone is utilised for its physiological action

4 Empirical therapy, the use of organic preparations *without any underlying scientific reasoning*

Bearing these four different methods in mind, let us turn for a moment to the consideration of the actual preparations in use

## Methods of Obtaining and Preparing Animal Extracts.*

The fresh glands or tissues of animals are secured, due care being taken to ensure that the species which has been proved most satisfactory for the particular extract is selected, and are freed from all connective tissue and fat The next step depends upon whether

| Organ | Animal Usually Used | Percentage of Dry Extract |
|---|---|---|
| Adrenal | Sheep | 20 |
| Duodenum | Pig | 15 |
| Hypophysis | Cattle | 22 |
| Kidney | Pig | 20 |
| Liver | Pig | 30 |
| Lung | Calf | 20 |
| …mmæ | Cow | 20 |
| …rve | Pig | 33 |
| …vary | Sow | 10 |
| …vary | Cow | 13 |
| …ancreas | Pig | 30 |
| …arathyroid | Horse | 22 |
| …lacenta | Ewe | 14 |
| Prostate | Horse | 20 |
| Spleen | Pig | 23 |
| Stomach | Pig | 20 |
| Testes | Bull | 12 |
| Thymus | Calf | 17 |
| Thyroid | Sheep | 25 |
| Thyroid | Cattle | 28 |

a total extract is required, or whether some part of the gland only is desired In the first case, the whole gland is dried *in vacuo*, which is the most rapid and satisfactory method, in the case of certain glands—*e g*, the pituitary, where the posterior lobe may be

* Quoted in substance from Harrower, pp 465–466.

required, or the suprarenal gland, where the medulla alone may be utilised—this is separated and isolated from the remaining tissue, and likewise dried *in vacuo* The accompanying table reproduced from Harrower's work shows the animal usually chosen, and the amount of moisture extracted during manufacture

The organic extracts may be taken by the patient in several different ways The actual gland may be consumed, but the amount taken is very uncertain A powder obtained from the dried gland is a more usual method, and it may be put up for convenience in compressed tablets, or into cachets or capsules Various alternative methods are in more or less general use—*e g*, the elixir, where the extract is sweetened and taken either alone or in combination All the recognised extracts are standardised, both physiologically and clinically

## Dosage.

In all books dealing with organotherapy a certain range of doses is given, and in the catalogues of manufacturers a dose which is designed to represent a uniform quantity of the extract is indicated It is important for everyone to realise the safe and suitable dose with which to commence the treatment in an individual case It is even more important for everyone unfamiliar with the use of these products to realise that the preparations in common use may roughly be divided into two groups those which are toxic in unsuitable doses and likely to produce unpleasant reactions, and those which are for practical purposes innocuous To present this principle in an easy form a table is appended

| Toxic Products | Average Dose. | Products not Usually Toxic | Average Dose |
|---|---|---|---|
| | Grains. | | Grains. |
| Suprarenal gland | 1–2 | Duodenum (secretin) | 1–3 |
| Adrenalin (1 in 1,000 solution) | 5–15 min. orally or injected | Intestine | 1–3 |
| Pituitary gland | 5 | Kidney | 5 |
| Parathyroid .. (A larger dose is given in some catalogues—*e g*, $\frac{1}{10}$ *to* $\frac{1}{4}$) | $\frac{1}{20}$–$\frac{1}{10}$ | Liver | 10 |
| Prostate .. | 1 | Lung | 2–5 |
| Thyroid .. (Larger doses are sometimes recommended) | $\frac{1}{10}$–3 | Lymphatic gland | 3–5 |
| Testes .. | 1–10 | Mammary gland | 5–10 (*circa*) |
| Ovary .. | 3–5 | Nervous tissue | 5 |
| Thymus (Or larger doses) | 5–15 | Pancreas | 5 |
| | | Pineal | 5–10 |
| | | Placenta | 5 |
| | | Spleen | 2–10 |

This table and the subsequent summary are intended as a rough guide to the various preparations, and are neither inclusive nor arbitrary

## Summary of Preparations.*

(*With Indications for their Use*)

EXTRACT—*Thyroid*—Dose, $\frac{1}{10}$ to 1, 2 to 5 grains By mouth or hypodermically

Hypothyroidism, myxœdema, cretinism, delayed development, toxæmias, obesity, constipation, menstrual disorders, skin diseases, neuroses, psychoses,

* Two different dosages are given in some cases The reason for this is that certain of the disorders for which a particular extract is prescribed require the smaller dose, others a dose within the larger range References to this subject will be found in the text

*Parathyroid* —Dose, $\frac{1}{50}$ to $\frac{1}{30}$, $\frac{1}{10}$ to $\frac{1}{2}$ grain By mouth or hypodermically

Paralysis agitans, tetany exophthalmic goitre, anxiety states (restlessness tremors, loss of weight), ? epilepsy

*Suprarenal* —Total extract, grains 1 to 2 Adrenalin (1 in 1 000), mins 5 to 15 By mouth or hypodermically

Hypoadrenia, Addison's disease, acute infections (*e g*, typhoid, cholera exanthemata), osteomalacia, tuberculosis, neurasthenia exhaustion states

*Pituitary* —1 Whole gland Dose, grains 1 to 5 By mouth

Acromegaly, hypotension, hypopituitarism, dyspituitarism constipation

2 Posterior lobe Dose, 5 to 15 mins By mouth or hypodermically

Uterine stimulation shock and collapse intestinal paresis amenorrhœa failure of lactation, diabetes insipidus

*Testes* —Dose grains 1 to 3 grains 5 to 10 By mouth or hypodermically

Exhaustion states (neurasthenia etc), impotence, obesity, hypopiesis defects of development (cryptorchism)

*Ovary* —Dose, grains 3 to 5 By mouth

Amenorrhœa, dysmenorrhœa disorders of the climacteric malnutrition infantilism neurasthenia

*Thymus* —Dose grains 5 to 15 By mouth

Exophthalmic goitre delayed development, rickets, *disordered calcium metabolism*

*Prostate* —Dose grain 1 By mouth

Melancholia and neuroses after prostatectomy. Prostatic hypertrophy

*Secretin* —Dose, grains 1 to 3 By mouth

Gastro-intestinal disorders, pancreatic insufficiency, steatorrhœa meteorism malnutrition from gastric or intestinal insufficiency diabetes mellitus.

*Intestine*.—Dose, grains 1 to 3 By mouth
Constipation, intestinal flatulence, colitis, enteritis.

*Kidney*.—Dose, grains 3 to 5 By mouth.
Uræmia, nephritis, albuminuria.

*Liver*.—Dose, grains 10 to 20. By mouth.
Hepatic insufficiency, glycosuria, constipation, intestinal intoxication

*Lymphatic Gland*.—Dose, grains 3 to 5 By mouth or hypodermically
Enlarged tonsils and adenoid growths, Hodgkin's disease

*Mammary Gland*.—Dose, grains 5 to 10 (*circa*) By mouth
Menorrhagia, metrorrhagia, fibroids, over-action of the ovaries

*Pancreas*.—Dose, grains 5 By mouth.
Diabetes mellitus, intestinal indigestion, tuberculosis, hyperadrenia

*Spleen*.—Dose, grains 2 to 10 By mouth or hypodermically
Infections, intoxications, tuberculosis, typhoid, splenomegaly, malnutrition,

*Pineal*.—Dose, grains 3 to 10
Defective development obesity

*Lung*.—Dose, grains 2 to 5 By mouth
Chronic bronchitis and emphysema, asthma, tuberculosis

*Placenta*.—Dose, grains 3 to 5 By mouth
Uterine subinvolution, lack of mammary secretion

*Nervous Tissue*.—Dose, grains 5
Functional nervous disorders (*e g*, neurasthenia, anxiety states, mental disorders) malnutrition, loss of weight

### Pluriglandular Products.

The state which has received the name "hypo-endocrinism" calls for a brief description, as it has been treated of recent years by the prescription of preparations manufactured from several of the internal secretory organs The disturbed functioning, theoretically due to a hormone deficiency, and dubbed hypo-endocrinism, is, in many ways, the lineal successor to neurasthenia, at all events so far as nomenclature is concerned The term may be unscientific, as it is certainly not exact, but in some ways it helps us to conceive some of the changes which may well underlie the features characteristic of nervous exhaustion If such secretions as that of the thyroid, suprarenals, pituitary, and gonads are requisite for good health and bodily strength, it is at least probable that the deficiency of one or more of them will lead to neurasthenia As we do not know which is the culprit in any given case, the practice of prescribing combinations of glands has gradually crept into use They have met with undoubted success, and their extensive use is a tacit acknowledgment that, certainly to some degree, deficiency of hormone-supply is present in these states

Many pluriglandular preparations are formed with a basis of nervous tissue, and include orchitic and luteal extract, and small doses of thyroid and pituitary Such a combination might be likened to the old-fashioned "mistura," where the main ingredients are the thyroid and pituitary, the orchitic appears in place of the syr glycerophosph co, and the nervous tissue is equivalent to "aq chlorof to the ounce"

This pluriglandular method has been called by Williams a "mitrailleuse," but there are many advocates of this method. In more indefinite states, where no single gland can be blamed, where the physiological effects of stimulation are arrived at, and when malnutrition is a feature, there is much to be said for the pluriglandular preparations. They have also been utilised in the treatment of dementia præcox and other psychoses, while a combination of other organs—*e g.*, spleen, liver, and pancreas—has been administered for digestive and metabolic disturbances, and as a means of reducing toxæmia.

## Hypo-endocrinism.

The endeavour of the physician, when considering hormone-therapy, in any given case, should be to have a clear idea in his mind as to the indications for a particular glandular extract, and also the action which this will exert in an individual case It is, perhaps, to be expected that pluriglandular therapy will lead to a somewhat haphazard method of prescribing, indeed, this has occurred in some instances, leading to confusion of thought and detriment to organotherapy as a whole

It is important to remember that, in this form of therapeutics, there are several ways of dealing with an abnormal functioning, just as there are several actions to be expected from the exhibition of one extract For example, the physician may decide that thyroid extract is indicated for its stimulating effect upon metabolism, or for its antitoxic and bacteriolytic powers, or for its stimulating effect upon other of the internal secretions, notably the adrenals and pituitary The state of thyroid in-

ility, to which Léopold-Lévi and Rothschild have
rred, and which I have called "thyroid wobbling."
a clinical condition deserving of recognition. Here
ere are outbursts of hyperthyroidism, but the
able condition is one of hypothyroidism. It will be
obvious that the exhibition of thyroid extract should
do good in these cases, by tending to remedy the more
permanent disorder. The difficulty is to recognise
such a case, unless the patient is under frequent
observation. But a disorder such as this may be
attacked from quite another angle—namely, by
discovering what is causing the disturbance of the
thyroid. The opinion is rapidly gaining ground
that a toxæmia is responsible for nearly all disturbances of this nature, and there is ample proof
that the toxæmia is often located in the bowel.
Adequate treatment to this viscus, then, would
enable the thyroid to adjust its secretion so as to
supply an even quantity of its hormone.

The term "hypo-endocrinism," although a philological monstrosity, has been used to describe those
"run-down" conditions which depend, theoretically,
upon deficiencies of the internal secretions which are
essential to normal metabolism. As this includes all
the recognised hormones, we must hypothesise a
diminution in the secretions of the thyroid, pituitary,
adrenals, gonads, digestive secretions, and others.

In spite, however, of the rather nebulous nature of
this theory, it is at least as definite as the current
beliefs and pathology of these disorders, the terms
"debility," "neurasthenia," "anæmia," all are used
loosely to indicate departure from health, to account
for which no organic basis can be found. Hypo-endocrinism, therefore, steps into the breach, and
suggests a tentative theory as to what is happening

metabolism. McCarrison says "The thyroid gland is to the human body what the draught is to the fire." Small doses of thyroid extract, incorporated with extracts of the gonads, should form a useful aid to metabolism An example of this has been given for men, the same firm manufacture a preparation for women

(ii)

| | |
|---|---|
| ℞ Pituitary | gr $\frac{1}{8}$ |
| Thyroid | gr $\frac{1}{6}$ |
| Ovarian } Mammary } | āā gr i |
| | (Oppenheimer) |

Although the ovarian and mammary glands are in some respects antagonistic, their dual employment as a metabolic stimulus has received some degree of support This combination is recommended for amenorrhœa, dysmenorrhœa, neurasthenia, hypochondria, and symptoms of the climacteric For the successful practice of organotherapy it is necessary to have a clear idea as to whether a single extract or a combination of extracts is the method of choice in any case These combinations can only be efficacious as an "adjuster" of a dislocated hormone-balance Where one symptom, such as amenorrhœa, is present, and where it appears to depend upon endocrine causation, the prescription of a single extract—for example, ovarian substance—is to be preferred

(iii)

| | |
|---|---|
| ℞ Adrenal gland | gr $\frac{1}{4}$ |
| Thyroid gland | gr $\frac{1}{12}$ |
| Spermin extract } Brain substance } | āā gr i |
| Calc glycerophosph | q s ad gr v |
| | (The Harrower Laboratory) |

This preparation may be regarded as an all-round tonic, and is suitable for asthenic cases, more especially those with a low blood-pressure, where the main trouble is mental and physical inertia The contra-indications for using any pluriglandular product containing adrenal or thyroid substance are the following. hyperpiesis, tuberculosis, glycosuria, sympathetic over-action, tachycardia, and the nervous restlessness and insomnia which characterise anxiety states In general terms, these are the disorders where such therapy is to be avoided

(iv)

| | |
|---|---|
| ℞ Elix colloid (Squire) | ♏x |
| Elix hypophysis cerebri (Squire) | ♏xxv |
| Syr glyceroph co | ʒi |
| Aq dest | ad ℥i |

℥i ter in die post cibos

The liquid preparations of thyroid and pituitary are useful when it is desired to graduate the quantity of each extract, or from time to time alter their relative proportions

(v)

| | |
|---|---|
| ℞ Elix colloid (Squire) | ♏xx |
| Collosal iodine (Crookes) | ʒi |
| Aq dest | ad ℥i |

℥i ter in die post cibos

The addition of an assimilable preparation of iodine to extract of thyroid is sometimes desirable Iodine is invaluable for patients suffering from endemic goitre In this prescription the collosal iodine is combined with the elix colloid., and may be used in all cases where iodine-therapy is indicated

### Practical Points in Hormone-Therapy.

From what has already been said, it will be seen that the indications which guide the physician in pluriglandular prescribing are frequently slight. The theory underlying hypo-endocrinism offers some grounds for combining organic extracts; and there are convincing reports of the efficacy of such a procedure from more than one authority. A theory has been suggested by Martinet which seems to explain many cases of this nature. He believes that there is a digestive disturbance which upsets the circulatory mechanism, forming a vicious circle. This syndrome he treats by means of secretin, administering at the same time some more potent endocrine product such as pituitary or thyroid. There is a beginning to every disorder, and there must be a point where functional disorder becomes structural or organic disease. Long-standing digestive disorder seems a likely precursor to metabolic abnormalities, which in turn may lead to diseases whose name is legion. Somewhere in this chain—it may be more cause than effect—will be found the internal secretions. Their balance, and the control they exercise as regulators of metabolism, becomes upset, and at this stage signs may be observed which are recognisable as of endocrine origin. But before this stage—indeed, in the beginnings of illness—it should be possible to intervene in such a manner as to stop the progress of the disorder; it ought to be possible to prevent one function after another from succumbing to the attack. This is, at present, merely theoretical rumination; but if one considers the progress of thyroid deficiency, from its

early stages to the full-blown myxœdema, one is made to realise what widespread degeneration might have been avoided if thyroid extract had been applied during the early stages. In like manner, the physician of the future may be able to step in before the disordered secretions have led to such states as gastroptosis, intestinal atony, nervous exhaustion, and Addison's disease, to mention a few disturbances to some extent dependent upon the internal secretions. Some approach to this desideratum can be made nowadays by the early diagnosis of such states as hypothyroidism and hypopituitarism. Small doses of the extract of these glands will sometimes put right a disturbance which other remedies have left untouched.

Intestinal stasis is a disorder which implicates the ductless glands in its stride, and which also offers a field for organotherapy. Putting aside for the moment the treatment of this condition by the usual remedies, we may consider what happens from the point of view of the internal secretions. That there is in many cases an ascending infection from the colon through the ileo-cæcal valve to the small intestine is admitted. Both the local and remote effects of this are likewise well recognised. The stomach and intestines develop an atony which causes sluggishness of their contents. This condition is accompanied by changes too widespread to be referred to here. We may mention a few of the more important. The constant drag of the prolapsed stomach and colon is, both subjectively and objectively, a source of disturbance. Gastric and intestinal indigestion is proof of disordered secretion, while infection of the pancreas, viâ Wirsung's duct, may lead to widespread metabolic disturbance. Finally the constant absorption

of toxins produces abnormalities ranging from pyorrhœa alveolaris to chronic invalidism

The adequate treatment of this syndrome calls for remedies other than organotherapy, and lubricants, abdominal support, diet, and vaccines, are only some of the therapeutic aids summoned to remedy this state But organic preparations may be useful, and should be considered in any case where endocrine disturbance is so obviously present Secretin, in virtue of its power to stimulate pancreatic digestion, is in high favour with some physicians Preparations containing this substance have been utilised in the belief that absence or diminution of this important digestive aid plays some part in the processes leading to constipation Fermentation in the small intestine is stated to be relieved by preparations of secretin, or by the administration of acid mixtures which stimulate the formation of a secretion from the duodenal mucosa In the belief that certain gastro-intestinal disorders commence by hypochlorhydria and diminished pancreatic digestion, leading to intestinal fermentation and ileac stasis, it is conceivable that ensuring adequate duodenal digestion would assist in rectifying the digestive abnormalities A preparation called *secretogen* has been utilised for this purpose, and one observer has stated that it is a most powerful excitant of gastro-intestinal secretion, and therefore indicated in cases showing intestinal paresis and indigestion

Extracts of the pancreas contain the ferments trypsin, amylopsin, and steapsin Pancreas substance can be administered where there is reason to suspect that pancreatic deficiency is sharing in the disorder The influence of the spleen on digestion has already been referred to, and is not so well

established as other of the organs we are considering

Williams has pointed out that the administration of thyroid extract to subthyroidic people will often regulate the bowels, but that the resulting motions are conspicuously light in colour. Pale stools, with or without steatorrhœa, are characteristic of pancreatic insufficiency. In such cases pancreatic extract with small doses of thyroid incorporated in a pluriglandular preparation might be found to be helpful

Extracts of bile should be referred to, as they have an undoubted action in increasing peristalsis. Biliary deficiency produces intestinal fermentation, with undigested fat and meteorism

Turning from the intestinal secretions, we find that help can be sought from several of the ductless glands situated further afield. Paramount is the thyroid. From what has already been said in this volume, it will be obvious that it exerts an action upon intestinal peristalsis. We have referred also to its utility in toxæmia. Here we will confine our attention to one or two fresh facts

Mutch has recently described the treatment of a series of cases of arthritis in which the primary cause appeared to be in the bowel. Adequate treatment was resorted to in all these cases, but in addition thyroid extract was prescribed with much benefit. Intestinal stasis damages the thyroid, and some of the symptoms of stasis may well be attributed to the thyroid. The relation of intestinal toxæmia and thyroid disturbance can be better understood since Kendall has shown that the active principle of the thyroid secretion is an iodine compound of indol, which in turn is a decomposition product of

tryptophan. An increased production of indol calls for its antidote, increased output of thyroid secretion.

This is the rationale of administering thyroid extract in stasis, and the results justify and prove the underlying theory. In addition to the thyroid, the pituitary has gained some little reputation in the organotherapeutic treatment of these patients. Pituitary extract stimulates the action of plain muscle, and has therefore been used in enteroptosis. It is possible that the efficacy which pituitary preparations undoubtedly possess in relieving headaches may be produced by stimulating excretion. In some instances of headache doubtless the relief is brought about by the power this extract possesses of raising blood-pressure. Pituitary extract dilates the renal vessels, and is therefore a diuretic.

I am inclined to think that a pluriglandular preparation containing small doses of thyroid and pituitary extracts, combined with a basis of adrenal substance, will be found helpful in those neurasthenic subjects with gastro-intestinal atony and a low blood-pressure. Such patients are usually wretchedly thin, with poor powers of assimilation, and consequently any treatment will probably be more efficacious if six weeks' complete rest in bed with adequate digestive and secretory aids is insisted upon, when the line of attack is settled.

The following represents the above combination:

| ℞ | | |
|---|---|---|
| | Desiccated suprarenal gland | gr. 1 |
| | Desiccated pituitary substance (whole gland) | gr. 1 |
| | *Desiccated thyroid gland* | gr. ½ |

(Parke, Davis and Co.)

It would be preferable, certainly, in some instances, to commence treatment with a smaller dose of

thyroid relative to the other constituents, say $\frac{1}{10}$ or even $\frac{1}{20}$ grain It should be remembered that the greater the need for thyroid appears, the smaller should be the initial dose, and the more cautiously it should be augmented The "driving power" of this extract is very great, and I have a patient under my care who is immediately upset by an increase from $\frac{1}{10}$ to $\frac{1}{4}$ grain In all such patients—that is to say, where thyroid intolerance is suspected—the dose should be regulated in tenths of a grain, until $\frac{4}{10}$ grain is reached It is certainly better administered in one dose at night

Finally, orchitic and ovarian extracts have their field of usefulness in the treatment of stasis and toxæmia It is stated that they promote oxidation, combat muscular weakness and exhaustion, reduce obesity due to suboxidation, and increase the body weight, where loss of weight is part of the syndrome This sounds too good to be true, but in speaking of thyroid extract in this relation it was pointed out that this extract reduces weight by increasing oxidation and increases weight by neutralising toxæmia Extracts of the gonads have a similar action, and, moreover, stimulate the other glands regulating metabolism

To sum up, then, organotherapy can assist in the treatment of stasis—

1 By supplying the internal secretions upon which digestion depends

2 By the administration of the "directors of metabolism"—namely, the thyroid, pituitary, and adrenals

3 By calling in the aid of the testicular and ovarian secretions

## Examples of Organotherapeutic Treatment.

However strongly empirical treatment is to be deprecated, its necessity is undisputed Not only does it offer, and has it supplied, the proof of many laboratory dicta, but many therapeutic aids have been born at the bedside. It is not maintained, I think, even by its most enthusiastic supporters, that organotherapy should do more than assist in the treatment of disease The day may come when the clinician has the ductless glands and their secretions so much in hand that he can check the exuberance or stimulate the laziness of an individual organ or a group of glands. At present we can assert a few facts dogmatically, and relate with due humility the results of our organotherapeutic procedures

There is small doubt that a working knowledge of organotherapy combined with a reasonable incredulity is the best combination Such a mental position enables us to give a patient the benefit of any knowledge which has been recently acquired, either from the laboratory or the bedside To say that organic preparations are useless and are merely expensive methods of experimenting, is, frankly, ignorant and prejudiced What about the acknowledged value of the thyroid in treatment? Or the parathyroid? If the case of parathyroid deficiency, published by Hurst, was the only example of the success of the extract it would be ample justification for further attempts to turn successful diagnosis into adequate treatment This patient resisted all treatment and became seriously ill, until parathyroid gland was tried, when he commenced to recover and became perfectly well and strong. This was the

only treatment which did any good in this instance, and therefore might be called a "specific"

If all physicians followed the doctrine that because there is no proof for many organotherapeutic procedures, therefore it is no use utilising them, little progress would be made, certainly in this branch of medicine

I will mention a few examples where ordinary methods have been valueless, but where organotherapy remedied—I will not say cured—the disorder A middle-aged man suffered from progressive loss of weight, associated with many subjective and a few objective symptoms No cause for this could be ascertained, despite repeated examinations by many physicians and the usual aids to diagnosis which the laboratory offers Eventually it became obvious that treatment must be initiated without further delay, as, if this had to be shelved until accurate diagnosis was arrived at, it might well be too long delayed

There was obviously a toxæmia, and one which interfered with metabolism Several more or less orthodox methods were tried, needless to say, rest, hyperalimentation, and intestinal stimulants failed to alleviate The weight continued to descend, and the digestion refused to avail itself of the extra milk, cod-liver oil, *et hoc genus omne* At this point, the sole guide to diagnosis was this, that the patient was unable to assimilate Unfortunately, the employment of the organic aids to digestion were equally unsuccessful, and made no difference to the patient's gastro intestinal abilities

I had been interested in the work which had been done recently by some observers—notably Schiff and Herzen—upon the spleen and its relation to digestion

These authors showed that pancreatic digestion was impaired or stopped when the splenic vessels were ligatured. Other evidence supports the view that the spleen is in some way concerned in digestion, and it occurred to me that perhaps extract of this gland might assist the grumbling pancreas to carry out its functions

A course of twelve injections of splenic extract were given, and the weight stopped descending, and a few pounds were gained The injections were then stopped, and ordinary medical measures continued. The improvement ceased and down went both the weight and the patient's spirits

A second course produced equally gratifying results, but the cessation of injections caused a relapse. However, after several courses of injections, the patient recovered, and now—two and a half years after he first commenced the treatment, and eighteen months since any injections were given—he remains well and strong, and his weight has increased by about 2 stones

Empirical, yes, but justified by results Perhaps one day it will be proved that the spleen is deserving of its large size, but that its work is so well hidden, or so indirect, that its function has remained obscure long after that of other organs concerned with digestion

Another example of unexpected relationship between a well-recognised syndrome and a fresh therapeutic aid is furnished by Jelliffe He records two cases diagnosed as tabes dorsalis by the clinical signs, in which thyroid extract brought about a cure, thus establishing these instances as examples of hypothyroidism Starkey has recorded striking results in the same disease by the repeated injection

of a pluriglandular product containing extracts of thyroid, pituitary, ovaries, and testicles Parathyroid extract alone has good results in other neuroses—namely, paralysis agitans, Yet its employment is based upon a slender foundation—to wit, that there is excessive loss of calcium in this disease, as in tetany, and that the excessive loss of calcium in the latter disease is brought about by parathyroid deprivation Therefore, supplying the extract of this gland may enable the body to retain more of its calcium, and prevent the tremors, etc, characteristic of the disease I have certainly found *it helpful in controlling the tremors, which, in some* instances, have been distinctly worse when the extract has been withheld But I have not seen any other good result from its use in this particular neurosis

But it may be helpful to add that I have frequently seen great benefit ensue when parathyroid extract has been prescribed for functional tremors, such as occurs in anxiety hysteria I have used this extract both orally and hypodermically, and have had no bad reactions

As an example of a difficult class of case, we have already referred to obesity and its relations to the thyroid gland Even adequate doses of thyroid, with careful diet and careful elimination, will frequently leave obese patients unrelieved Increasing the dose of the thyroid does not always improve the condition But on several occasions I have found that the addition of pituitary extract has been crowned with success where the other measures alone were useless

℞ Thyroid extract .. .. .. gr ¼
Pituitary (whole gland) .. .. gr ¼
Orchitic extract } .. .. āā gr. ½
Adrenal extract }

One or more twice or three times a day after meals

The above represents a combination which should stimulate metabolism Given in this way, it is capable of increase as seems desirable

One patient suffering from obesity was easily reduced to satisfactory size by thyroid alone, with some slight dietetic modification Another showed no improvement until pituitary extract was given. A third—an example of bursts of hyperthyroidism with an underlying hypothyroidism—could only take small doses of thyroid alone, but reached a more satisfactory dose when a pluriglandular preparation was given

The treatment of impotence is deserving of mention here As a rule it is the accompaniment of some more general deficiency, and not a disease *per se* In the case of hypoparathyroidism already referred to, sexual power only returned after six months' administration of the extract In some cases impotence is an accompaniment of bodily weakness, but sometimes is accompanied by an otherwise normal system For this reason no single extract can be recommended for this symptom I have been disappointed with extracts of the gonads, perhaps they have been given in unsuitable cases

It is usually advisable to try and account for the symptom from the endocrinological standpoint—that is to say, to search diligently for signs of disturbance among the internal secretory glands Thyroid extract has, in my experience been more helpful than gonadic, pituitary has also earned my

gratitude I have had no experience of pineal gland, although theoretically it might possibly be helpful in some cases

It must be remembered that this condition is often reached by the psychotherapist, without the aid of medicines But the synergistic action of the thyro-parathyroid system is not to be despised

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A few words about Graves' disease and organotherapy Williams has pointed out that tubercle and Graves' disease are two disorders in which thyroid extract should not be given He has also drawn attention to the similarity of the two types The sufferers from both these disorders are usually thin, with moist, smooth skins, ample hair, both on the head and trunk, restless, nervous, emotional, and changed in their mental outlook

Williams refers to the intramuscular injection of bile-salts as a possible treatment for exophthalmic goitre, on the ground that the clinical pictures of jaundice and myxœdema have several features in common He also says that the preparation he has used was, significantly enough, first introduced for the treatment of tubercle

We will not refer in detail to the methods in general use for the treatment of Graves' disease While, speaking generally, thyroid extract is unsuitable for these patients, I think that there are instances where its cautious use might be beneficial. Small doses, carefully watching for reaction, should help to take some of the strain off the gland, but only in those cases where there are general signs of an underlying deficiency, and these are usually the milder cases. Usually, of course, its employment in these cases is

only productive of harm. Neither do I think that any help can be relied upon from extracts of the gonads. Adrenal extract, also, is generally admitted to be useless or harmful But I have had good results from pituitary extract in some patients, and thymus extract should certainly be given a trial.

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Nocturnal enuresis is sometimes dependent upon an underlying thyroid deficiency. In these cases the exhibition of thyroid extract is a specific treatment. The dose should usually commence with $\frac{1}{4}$ grain at night, increased until the patient is receiving $\frac{1}{2}$ grain twice daily If no improvement is seen after six weeks' medication, the treatment should be discontinued, unless there are other signs of hypothyroidism If thyroid extract alone fails to relieve the condition, small doses of pituitary should be tried, as this combination has been favourably reported on where thyroid alone has failed

Another symptom which can be treated by thyroid extract is pruritus This is a constant feature of jaundice, and as we have already indicated, jaundice and myxœdema share certain clinical characters in common It has been shown that the administration of thyroid causes the disappearance of bile-salts from the urine, also that after ligature of the bile-duct the colloid in the thyroid gland increased, which has been regarded as a possible defensive mechanism against biliary intoxication

This extract, therefore, can be given in the pruritus of jaundice with some confidence that it will produce relief It has also been recommended for the treatment of eclampsia, on the same reasoning.

Among the stigmata of subthyroidism more

particularly noticeable in children are relaxation of the articular ligaments, producing "double joints," and tending to the production of spinal lordosis, knock-knee, flat-foot, etc. Delayed sexual development, the presence of adenoids, enlarged tonsils, constipation, imperfect control of the sphincter vesicæ, undue fat formation, and stunted growth, may be taken as suggestive that the thyroid has found the strain imposed upon its resources by the growing child more than it could meet. Small doses of the extract should be considered in these cases, it will frequently be found to lead to better bodily health

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As we review the present stage of development of organotherapy, we are bound to admit that vast territories remain to be explored and conquered in this realm of therapeutics A working knowledge of the physiology of the internal secretions is essential to its practice, and success in the administration of organic products depends largely upon whether the prescriber carries in his mind the functions of the various glands, extracts of which he is administering In infancy, in adolescence, in adult life, the task of the doctor is rendered easier if he adds to his weapons the glandular extracts with which nature regulates metabolism and fights disease

This little book endeavours to point the way to success in the application of organotherapy Until our knowledge of the bodily processes is more complete, until, indeed, we know more of the factors which go to produce and maintain health, many therapeutic procedures will remain more or less speculative The psycho-physical mechanism of the

human being is too complicated for any single c
to remain single or even to lead to a single effect

In organotherapy, as much as in any forn
treatment, this fact deserves recognition V
recognised it should be remembered, and v
remembered it should be acted upon.

# BIBLIOGRAPHY

**Organo-Therapy: or Treatment by Means of Preparations of Various Organs.** By H Batty Shaw, M D (Lond.), F R C P Cassell and Co, London

**The Endocrine Organs.** By E A Schäfer Longmans, Green and Co, London

**Practical Hormone-Therapy.** By H R Harrower, M D Baillière, Tindall and Cox

**The Internal Secretions.** By E Gley Translated by M Fishberg W Heinemann

**The Organs of Internal Secretion.** By I Geikie Cobb Third Edition Baillière, Tindall and Cox, London.

**New Aspects of Diabetes** By Professor Carl von Noorden, Vienna Wright, Bristol

**Glycosuria and Allied Conditions.** By P J Cammidge, M D (Lond) Arnold London

**The Pituitary Body and its Disorders** By Harvey Cushing, M D Lippincott Philadelphia

**The Diseases of the Ductless Glands for Practitioners of Medicine and Surgery** By S P Beebe, Ph D, M D (Phil)

**The Nervous and Chemical Regulators of Metabolism** By D Noel Paton, M D B Sc Macmillan, London and New York

**Glandes Surrénales et Organes Chomaffines** By Lucien et Parisot Gittler, Paris

**Dieases of the Thyroid Gland.** By George R Murray, M A M D Lewis, London

**Physiological Principles in Treatment.** By W Langdon Brown Baillière, Tindall and Cox

**Internal Secretion and the Ductless Glands.** By Swale Vincent, M D., D Sc. Arnold, London

**The Internal Secretory Organs: their Physiology and Pathology.** By Professor Dr Arthur Biedl With an *Introductory Preface by Leonard Williams, M D., M.R C P* Translated by Linda Forster

**The Internal Secretions and the Principles of Medicine.** By Charles de M Sajous, M D, LL D. Davis, Philadelphia, Phillips, London

**The Thyroid Gland in Health and Disease.** By Robert McCarrison Baillière, Tindall and Cox, London

**Medical Diseases of the War.** By A F Hurst Arnold, London

**Vagotonia: A Clinical Study in Vegetative Neurology.** By Eppinger and Hess Translated by W. M Kraus and S. Jelliffe New York.

## ARTICLES

**Dustin:** Quelques mots à propos du thymus humain *Ann. et Bull Soc Royale Sci Méd et Nat* (Bruxelles) 1919.

**Klose (H.) and Vogt (H.):** Klinik und Biologie der Thymusdruse (Tübingen) 1910

**De Cyon (E.):** Les functions de l'hypophyse et de la glande pinéale (Paris) 1907.

**Dana (C. L.) and Berkeley (W. N.):** The Functions of the Pineal Gland *Med Record* (New York) *1913*, lxxxiii, 835

**Renan and Delile:** De l'utilité d'associer les médications opothérapiques *Pr Méd* (Paris), *1907*, xv., 391.

**Vidal (E.):** Essai de thérapeutiques cellulaire, opothérapie ganglionnaire *Pr Méd* (Paris), 1905, xxi, 907.

**Starkey (F. R.).** The Combined *Use of Thyro-parathyroid*, Pituitary Ovarian, and Testicular Extracts *New York Med Journ* 1912 xcv, 1257

**Dercum (F. X.) and Ellis (A. G.):** The Examination of the Ductless Glands in Dementia Præcox *Journal of Nervous and Mental Diseases* (Boston), 1913, xl, 73

Moorhead (T. G.): The Action of Lymphatic Extracts *B M J* (suppl), 1906, ii, 12

Blair Bell (W.): The Relation of the Internal Secretions to the Female Characteristics and Functions in Health and Disease *Proc. Roy Soc. Med.* (London), 1913, vii, 471

Blair Bell (W.): The Genital Functions of the Ductless Glands in the Female *Lancet* (London), 1913, i, 809

Williams (Leonard): The Therapeutic Promise of the Internal Secretions *Practitioner* (London), November, 1911.

White (J. A. H.): Cottonseed Extract and Pituitary Extract during Lactation *Practitioner* (London), 1913, xci, 422.

Miller (J. L.), Lewis (D. D.), and Mathews (S. A.): The Effects of Extracts of the Different Parts of the Hypophysis *Proc Am Physiol Soc* (Boston), 1911, xxvii, p. xvii

Williams (Leonard): Pituitary Extract and Some of its Effects *Clin. Journ* (London), 1910, xxxvi, 92

Bidwell (L.): Investigation into the Effect of Pituitary Extract on the Bowel after Abdominal Operation *Clin Journ* (London), 1914, xxxviii, 331

Williams (Leonard): Discussions on the Therapeutic Value of Hormones *Proc Roy Soc Med* (London), 1914, vii, 32

Dale (D. D.): Discussions on the Therapeutic Value of Hormones *Proc Roy Soc Med* (London), 1914, vii, 34

Dor (H. and L.): Du traitement de la maladie de Basedow par le thymus *Lyon Méd*, 1907, cviii, 19

Paton (Noel): The Relation of the Thymus to the Sexual Organs *Journ Physiol* (London), 1905, xxvii, 28.

Langmead (F): Alimentary Toxæmia in Relation to the Thyroid Gland *Lancet*, 1913, i, 1312

Hutchison (R): On Some Disorders of the Blood-forming Organs in Early Life *Lancet*, 1904, i, 1323

**Harrower (H. R.)**: The Therapeutic Action of Splenic Extract and its Application in the Treatment of Tuberculosis. *Lancet*, 1913, i, 524

**Bosanquet (W. C.)**: Some Considerations on the Nature of Diabetic Methods *Lancet*, 1905, i, 977

**Harrower (H. R.)**: Neurasthenia, an Endocrine Syndrome A monograph. *The Harrower Laboratory.*

**Bram (I.)**: Exophthalmic Goitre and Surgery. *New York Med. Journ.*, 1921, cxiii, 266

**Jeliffe (S. E.)**: Hypothyroidism and Tabes Dorsalis *New York Med. Journ.*, 1921, cxiii, 383

**Marie (A.)**: Opotherapy in Basedowism *Bull Gén Thérap* (Paris), 1921, clxxii, 439

**Marine (D.) and Kimball (O. P.)**: The Prevention of Simple Goitre in Man *J Am Med Ass.* (Chicago), 1921, lxxvii, 1068

**Morris (M. F.)**: *Med Record* (New York), 1921, xcix, 133

**Utley**: Some Suggestions for the Treatment of Hyperthyroidism. *Penn Med. Journ* (Philadelphia), 1921, xxiv, 541

**Wuth (O.)**: The Biological Effects of Proteinogenous Amines *Biochem Ztschr* (Berlin), 1921, cxvi, 237.

***Cameron (A. T.) and Carmichael (J.)***: The Comparative Effects of Thyroid and of Iodide Feeding on Growth in White Rats and Rabbits *Journ Physiol* (London), 1921, lxxiv., 54

**McGraw**: Myxœdema *Journ Mich Med Soc* (Grand Rapids), xx, 27

**Rogers (J.)**: *Med Record* (New York), 1920, xcviii, 631.

**Geikie-Cobb (I.)**: The Thyroid Gland. some clinical observations (*New York Med Journ*), April, 1922

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